HRCT in Interstitial Lung Disease

Instructive Case Studies

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ISBN 978-3-030-16314-3 ISBN 978-3-030-16315-0 (eBook)
https://doi.org/10.1007/978-3-030-16315-0

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Volenti nihil impossibile
Nothing is impossible to him who has the will

Foreword

I was pleased to read and, with several notes and recommendations, review the following text, which covers the radiological diagnostic aspects of lung disorders using HRCT within adults. Apart from the successful chapters of J. Polak, found in the first and second editions of Professor Vasakova's book on interstitial pulmonary diseases, this is a complete modern work of challenging problematics. Positive is the cooperation of the authors, as this book was created with the contributing work of radiologists and respiratory physicians from three important Czech institutes—University Hospital Hradec Králové, University Hospital Olomouc, and Thomayer Hospital. An important message that is illustrated throughout the whole text is the fact that today's diagnostic and decision-making process in patient care is based on consensual conclusions following a direct discussion within a multidisciplinary team consisting of a respiratory physician, a radiologist, and a pathologist.

I consider the curriculum of the book to be very successful in terms of meeting the main educational goal—increasing the knowledge for recognising basic abnormal images (morphs or patterns) and their use in clinical-radiological differential-diagnostic balances. In general, the clinical aspects of disease diagnosis are briefly analysed, and further, the basics of interpreting HRCT findings are sufficiently presented. I can see a special systematic approach in dividing the individual diseases according to the dominant patterns—decreasing density (cysts, emphysema, etc.) and increasing density (linear opacity, knots, shadowing of ground glass, and the consolidation of lung tissue). In this way, almost 50 cases are analysed in detail, all of which can be very well understood and practised. The book is aimed primarily at radiologists (I myself consider it the basic text for confirmation) and respiratory physicians, but it will also be appreciated by colleagues from other fields—pathologists, rheumatologists, other internists, immunologists, etc. It enjoys a great format and high-quality graphics, which is most convenient when recognising radiological findings in such rich images.

Congratulations to the primary author Eva Kocova MD, PhD, and to her other collaborators for a successful piece. Are you afraid of interpreting HRCT of the lungs? Do not buy a teddy bear, but start studying this book! In addition to all of

that, I hope you acquire a pleasant sentiment towards this field of imaging, which has a definite logic, starting already in the form of a secondary pulmonary lobule that can be controlled without fear!

Hradec Králové, Czech Republic Pavel Elias
4 April 2018

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Acknowledgments

The book was supported by an unrestricted educational grant from Boehringer Ingelheim.

I would like to offer my special thanks to Punnam Mittu, MD; Ian McColl, MD; and Barbora Novotna, MD for their technical support.

Contents

About the Authors

Vladimir Bartos, MD was born on 2 February 1976 in Hradec Králové. After he finished the grammar school in Nový Bydžov, he graduated from the Faculty of Medicine of Charles University in Hradec Králové in 2000. After graduation, he joined the Department of Pulmonology at the University Hospital in Hradec Králové, where he works until now. In 2004, he was certified in Internal Medicine and in 2007 in Pneumology and Phthisiology. In addition, he completed specialised training in bronchology and functional lung examination. Since 2006, he has been working as the head of ambulance, day-care centre, and functional laboratory of the Department of Pulmonology. He specialises in the care of patient on the long-term home oxygen therapy and also concentrates on patients with interstitial lung diseases. He works in bronchology and the functional lung lab. Since 2007, he has been working as an internal quality auditor at the University Hospital in Hradec Králové according to accreditation and certification of national standards of SAK CR.

He is a member of the Czech Pneumological and Phthiseological Society (member of the Functional Pulmonary Diagnostics Section, Interstitial Pulmonary Diseases Section, and the Lung Transplantation Section) and the European Respiratory Society. He is the coresearcher of several clinical studies and co-author of several publications and articles. His main professional interests are bronchology, functional lung examination, oxygen therapy, and interstitial lung diseases.

Filip Ctvrtlik, MD, PhD was born on 16 February 1975 in Olomouc. In 1989–1993, he studied at Jiri Wolker Grammar School in Prostejov. Due to his love for animals, he joined the University of Veterinary and Pharmaceutical Sciences Brno at the Faculty of Veterinary Hygiene and Ecology in 1993. However, in order to avoid the risk that he would eventually end up working in a slaughterhouse, he decided to fundamentally change his field. So, in 1994 and 1995, he worked as an educator at Don Bosco's Silesian Youth Center in Ostrava. In 1995–1997, he attended postgraduate studies at the Emanuel Pötting Post-Secondary Medical School in Olomouc, Department of Radiological Laboratory, and there his fascination for medicine grew. In 1997, he was admitted to the Faculty of Medicine of the Palacký University in Olomouc. He successfully completed his studies in 2003.

In 2003, he joined the Department of Internal Medicine III, Faculty Hospital, in Olomouc. In order to learn about the inner beauty of his patients, he decided to

devote himself to imaging methods, and in 2004, he joined the Department of Radiology of the Faculty Hospital in Olomouc, where he has been working as a secondary physician until now. In 2008, he defended his dissertation thesis on "Imaging Methods in the Diagnosis and Treatment of Adrenal Tumors". In 2009, he successfully ended his residency in radiology and imaging methods. He is an assistant professor of undergraduate and postgraduate radiology teaching at the Faculty of Medicine and Dentistry of the Palacký University in Olomouc. He leads medical students in their scientific and professional activities and at the same time coordinates postgraduate studies. He is a member of the Czech Radiological Society and the American Roentgen Ray Society.

His specialisation is thoracic and urogenital radiology, where he closely cooperates with the Urological Clinic and especially with the Clinic of Pulmonary Diseases and Tuberculosis. He is the author of Czech and foreign publications, including publications with an impact factor.

He has an amazing wife, Liduska, and wonderful active children, Marketka, Honzik, and Hanicka.

Eva Kocova, MD, PhD was born in Bruntál on 1 November 1978. After graduating from high school, she was admitted to the Faculty of Medicine of Charles University in Hradec Králové. She successfully completed her studies in 2004. Before, she spent 3 months at the Mayo Clinic in Minnesota in Gastroenterology. After her studies, she started to work at the Department of Radiology of Chrudim Hospital. She gained specialised competences in radiology in 2011. In May 2012, she joined the Department of Radiology of the University Hospital Hradec Králové, where she concentrated on pulmonary and urgent radiology. In 2017, she completed her postgraduate studies. The topic of her dissertation was "Phenotype assessment of patients with a severe form of chronic obstructive pulmonary disease using HRCT of chest". Her main field of professional interest is interstitial lung diseases. She attends a number of radiological and pulmonary congresses, where she often lectures as an invited speaker. She is the author and co-author of several publications in impact journals. She is a member of the Czech Radiological Society and European Society of Thoracic Imaging. Until 2019 she is ESTI DIPLOMA holder.

She is married and has two children. She likes to spend her free time with her family in the forests of Hradec Králové and in the Orlicke Mountains.

Vladimíra Lostakova, MD, PhD was born on 16 November 1959 in Dacice. Both parents were doctors. In 1978, she finished her grammar school final examinations in Olomouc and then studied at the Faculty of Medicine and Dentistry at the Palacký University in Olomouc. She graduated in 1984 and then joined the OUNZ Olomouc in 1985. In 1989, she obtained an attestation from Internal Medicine. In 1991, she joined the Department of Respiratory Medicine in the University Hospital in Olomouc, and in 1994, she obtained an accreditation in tuberculosis and respiratory diseases. As a pneumologist, she mainly deals with interstitial pulmonary diseases, pneumological cytology, and especially the evaluation of bronchoalveolar fluid with a focus on interstitial lung diseases. The topic of her doctoral study was the

importance of examining tumour markers CYFRA 21-1, NSE, TPA, and CEA in bronchoalveolar fluid in diffuse interstitial diseases.

She is a member of the Interstitial Lung Diseases Section. She also works as an assistant professor and participates in the teaching of students at the Faculty of Medicine and Dentistry of the Palacký University in Olomouc. She has two sons. Her older son graduated from the Faculty of Science, and her younger son is an orthopaedist who also works at the University Hospital in Olomouc. Her husband is an engineer-economist and works at the Regional Office in Olomouc. Her hobbies include classical music, theatre, cycling, and traveling. She is the author of a number of publications in the field of tuberculosis and respiratory diseases, particularly with a focus on interstitial lung diseases.

Martina Sterclova, MD, PhD was born in 1979 in Klatovy. She finished the grammar school in 1998, and then in 2004, she graduated at the Faculty of Medicine of Charles University in Hradec Králové. After graduation, she joined the Department of Respiratory Medicine of Thomayer Hospital, initially at a department in Prosečnice and then in Prague. In 2009, she passed her accreditation in the field of tuberculosis and respiratory diseases and defended her doctoral thesis on "Chemokines and their receptors in the pathogenesis of ILD". Since 2008, she has been working as an assistant in the First Faculty of Medicine of Charles University in Prague and also participates in postgraduate education of the doctors, especially in the field of pneumology. She is a member of the Czech Pneumological and Phthiseological Society and the European Respiratory Society. She is also engaged in scientific activities, primarily with a focus on the pathogenesis of interstitial lung diseases. She regularly publishes in Czech and foreign professional journals and actively participates in Czech and international congresses.

Martina Vasakova, MD, PhD was born in Prague on 20 September 1964. She was the first child of a professor of mathematics and descriptive geometry and Tesla researcher in the field of television and shortwave broadcasting. She attended primary school with extended language learning at the Cuban Square in Prague. At the age of 13, she was admitted to Wilhelm Pieck Grammar School. She was expected to go to the renowned mathematical class, but she had chosen languages. In 1982, she passed the entrance examinations for the First Faculty of Medicine of Charles University. At that time, however, she was unsuccessful in her application due to what was then deemed to be a "politically incorrect political background", but upon a ministerial appeal, she was accepted into the medical programme—from which she graduated in 1988. During her studies, she met her husband, Jaroslav, and gave birth to their first child, her daughter Terezka. At the age of 23, she joined the Research Institute of Tuberculosis and Respiratory Diseases (VÚTRN, later Department of Pneumology and Thoracic Surgery) in Bulovka, where she stayed until 1999. In 1990, she gave birth to her second child—son Jindřich. She obtained three postgraduate qualifications—the first one from Internal Medicine in 1992, the second qualification from the Institute of Tuberculosis and Respiratory Diseases in 1995, and the third one from Allergology and Clinical Immunology in 1999. She

was taught bronchology in VÚTRN by Frantisek Fiser and Jiri Patek. With Frantisek Fiser, she shared a medical room after arriving at VÚTRN. In 1993, she completed a bronchology course at The First Clinic of Tuberculosis and Respiratory Diseases, in Katerinska, under the supervision of Vasil Bohut, and later became the holder of a full license for interventional bronchology.

On 1 January 2000 (at the age of 36), she became the chief of the then newly established Institute of Pulmonary Diseases (now the Department of Respiratory Medicine of the First Faculty of Medicine of Charles University) of Thomayer Hospital, which was the head department in Prosečnice. In 2005, after a union between the departments in Prosečnice and Krc, she left her post in Prosečnice to take up the appointment of chief of the united main Department of Respiratory Medicine already based only in Krc. In 2016 onwards, she became the head of this department.

As part of further scientific education, she graduated in 2007 from a postgraduate study in the field of immunology at the First Faculty of Medicine of Charles University. In 2008, she remained in the field of internal medicine within the same faculty, and by 2015, she was appointed a professor in the same field.

Since the beginning of her career, she has also been involved in undergraduate and postgraduate education. In 1992–1996, she was an external assistant of the Third Faculty of Medicine of Charles University and in 1996–2000 a full assistant at the same faculty. In 2003–2008, she worked as an assistant professor at the First Faculty of Medicine of Charles University; in 2008, she started to work there as an associate professor and in May 2005 as a professor. She has been teaching and lecturing within postgraduate education for internists, pneumologists, and students of Nursing since 1999.

She is a tutor of PhD studies in the field of immunology at the First and Third Faculty of Medicine, human physiology and pathophysiology at the First Faculty of Medicine, and experimental surgery at the Third Faculty of Medicine and also an immunology tutor for master studies in the Science Faculty.

She is a member of the Czech Pneumological and Phthiseological Society (ČPFS), Czech Internist Society, Czech Immunological Society, Czech Society of Allergology and Clinical Immunology (ČSAKI), European Respiratory Society (ERS), American Thoracic Society (ATS), European Academy of Allergy and Clinical Immunology (EAACI), World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), and European Society for Tuberculosis (TB NET). In 2010, she was elected to the ČPFS Committee and became a coordinator of the field of pneumology and phthisiology for the Capital City of Prague. She is the chairwoman of the Interstitial Lung Disease Section of ČPFS. Within the EAACI, she was elected to the Asthma Section Board in 2017.

She is a researcher and coresearcher on a number of research projects focused on interstitial diseases and tuberculosis. She is also the coresearcher of international grants and research projects: RESOLVE, GenPhenReSa, IPF NET, Global IPF Collaborative Network, ERN, and CHILD-COST. She is a member of the Editorial Board of *Respirology* and *Studia Pneumologica et Phthiseologica*, editor of *BMC*

Pulmonary Medicine, and a reviewer for a several of the European and American journals. In 2016, she won the Czech Republic Innovation Award for the invention of a biodegradable tracheal stent.

She is the author of many Czech and foreign publications, including articles in journals with an impact factor, where mostly the articles that focused on genetics and the phenotype of interstitial lung diseases are repeatedly quoted. She lectures at domestic, foreign, and international pneumological and allergy congresses. She collaborates on creating textbooks for medical faculties and postgraduate education. Apart from her daily duties and tutoring, she is also involved in research project proposals and scientific cooperation with domestic and European scientific and clinical workplace. Her professional interests are interstitial lung diseases, immunology of lung diseases (asthma, interstitial lung diseases), and interventional bronchology.

In her personal life, she tries to spend her free time with her whole family and friends (including her cat named Daduska). Her main hobby is music and singing, especially rock and heavy metal. She graduated from a music school in piano and then classical guitar, but she does not have the time to play actively. She likes reading and going to the theatre and cinema. She likes concerts of classical and even non-classical music. She loves warm climates and the sea. She likes walking and running. She prefers to go on foot whenever it is possible. She practises yoga. In winter, she takes her husband skiing and skating.

P.S. She loves life with all its challenges and the adversities that it brings.

Jana Votrubova, MD, CSc was born in Prague. She graduated from the First Faculty of Medicine of Charles University in Prague in 1985. After graduation, she joined the Department of Internal Medicine of the Hospital in Vejprty, OÚNZ Chomutov, in the North Bohemian Region. After several years at OÚNZ Mlada Boleslav and NsP Kralupy nad Vltavou and OÚNZ Mělník, she returned to Prague to the Radiology Department of the First Faculty of Medicine of Charles University and the General Teaching Hospital. There she stayed for 10 years. In 2003, she started to work at the developing team of the first hybrid device in the Czech Republic at the Na Homolce Hospital, where she spent 5 years exclusively at PET/CT. After 5 years, she partially worked at magnetic resonance and partially at PET/CT. She was working abroad at the NHS Dumfries and Galloway for 2 years. In 1992, she received a first degree certificate in the field of radiodiagnostics and in 2006 a second degree certificate in the same field. She defended her candidacy work in 2001. Since 2012, she has been chief of the Department of Radiology of Thomayer Hospital in Prague. Her main areas of interest include oncological and oncosurgical radiodiagnostics. During her professional life, she participated in the first radiofrequency ablations of liver tumours in the Czech Republic and in particular in the introduction of the first PET/CT hybrid device in the Czech Republic.

She is a member of the Radiological Society of CLS JEP where she has been the vice-chair for 10 years. She is an active member of the European Society of Radiology and the European Society of Gastrointestinal and Abdominal Radiology.

She is the author of the monograph *Clinical PET and PET/CT* (Galen 2006) and co-author of several professional publications. A dozen times she lectured in the Czech Republic and abroad. She is the leading project executor of one grant and several clinical studies.

Monika Zurková, MD, PhD graduated from the Faculty of Medicine and Dentistry of the Palacký University in Olomouc, specialising in general medicine, in 1996. After graduating, she started to work at the Department of Respiratory Medicine at the University Hospital in Olomouc, where she works until now. She successfully obtained accreditations of the first degree from Internal Medicine in 1999, and in 2008, she received the Pneumology and Phthisiology certificate.

She has also graduated from specialised education in sleep medicine. She works as an assistant professor of general and dental medicine in the Czech and English study programmes. She is a lecturer of student scientific work. She defended her dissertation on the topic "Characteristics of Generalized Sarcoidosis" in 2015. She is the author of several clinical studies and professional articles and co-author of recommended procedures and publications. Her main professional interests are interstitial lung diseases and work in the sleep medicine laboratory. She is a member of the Czech Pneumological and Phthiseological Society, Interstitial Lung Diseases Section, and Czech Society for Sleep Research and Sleep Medicine.

Abbreviations

AFOP	Acute fibrinous and organising pneumonia
AIP	Acute interstitial pneumonia
AP	Angina pectoris
ARDS	Acute respiratory distress syndrome
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
COP	Cryptogenic organising pneumonia
COPD	Chronic obstructive pulmonary disease
CP	Cyclophosphamide
CPFE	Combined pulmonary fibrosis and emphysema
CT	Computed tomography
CTA	CT angiography
DAD	Diffuse alveolar damage
DAH	Diffuse alveolar haemorrhage
DIP	Desquamative interstitial pneumonia
DLco	Diffuse lung capacity for CO
DM	Diabetes mellitus
EAA	Exogenous allergic alveolitis
EBB	Endobronchial biopsy
EBUS	Endobronchial ultrasound
EBV	Epstein-Barr virus
EGPA	Eosinophilic granulomatosis with polyangiitis
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GG	Ground glass
GGO	Ground glass opacity
HA	Heart action
HRCT	High-resolution computed tomography
ICD	Implantable cardioverter-defibrillator
ICS	Inhaled corticosteroids
IHD	Ischaemic heart disease
IL	Interleukin
ILD	Interstitial lung diseases

IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
IRI	Immunoreactive insulin
K_{CO}	Transfer coefficient
LABA	Long-acting beta-agonists
LAM	Lymphangioleiomyomatosis
LE	Lower extremities
LIP	Lymphocytic interstitial pneumonia
LTOT	Long-term oxygen therapy
MDT	Multidisciplinary team
MEF50	Maximal expiratory flow at 50%
MI	Myocardial infarction
MIQ	Myocardial infarction Q type
MPR	Multiplanar reconstruction
MRI	Magnetic resonance imaging
NSIP	Non-specific interstitial pneumonia
OP	Organising pneumonia
PAP	Pulmonary alveolar proteinosis
PCR	Polymerase chain reaction
PLCH	Pulmonary Langerhans cell histiocytosis
PPFE	Pleuroparenchymal fibroelastosis
RB-ILD	Respiratory bronchiolitis-associated interstitial lung disease
Ref. v	Reference value
RTX	Rituximab
RV	Residual volume
SACE	Serum angiotensin-converting enzyme
SCTD	Systemic connective tissue diseases
SLE	Systemic lupus erythematosus
SMRP	Soluble mesothelin-related protein
SRIF	Smoking-related interstitial fibrosis
TB	Tuberculosis
TBB	Transbronchial biopsy
TBLB	Transbronchial lung biopsy
TIA	Transient ischaemic attack
Tiff.	Tiffeneau-Pinelli index FEV_1/VC
TLC	Total lung capacity
TNF	Tumour necrosis factor
UE	Upper extremities
UIP	Usual interstitial pneumonia
US	Ultrasound
VATS	Video-assisted thoracoscopic surgery
VC	Vital capacity

Part I

General Part

Introduction

1

Martina Vasakova

Interstitial lung disease (ILD) describes a very comprehensive variety of pulmonary disorders of differing aetiology. As ILD can affect all the compartments of the lung and usually affect both lungs, they are also termed diffuse parenchymal lung disease. More specifically, an ILD is understood as a diffuse lung disorder arising on an inflammatory or fibro-proliferative basis, or a combination of both. In addition, tumorous and infectious lung diseases may also mimic diffuse pulmonary disorders, and it is sometimes difficult to distinguish these from other inflammatory and fibrotic processes.

The recognition of specific entities in the vast forms of ILD is not straightforward, and it requires the ability to combine individual clinical, laboratory, radiological and histopathological findings. Based on this combination one can determine either the definitive diagnosis or at least the character of the lung disorder, and thus significantly narrow the differential diagnosis. The topic of ILDs has until recently attracted only fans with an interest in unexplored, problematic and unusual cases, as treatment for many of these diseases was unavailable. In addition, there was a general awareness that they were uncommon or even a rare diagnosis. However, if the possibility of an ILD is taken into account when considering the symptoms that lead to a differential of pulmonary disease, we then suddenly find more cases that would have otherwise been missed, or possibly mistaken for another diagnosis, often until the death of the patient. The breakthrough of treatment for one of the most serious interstitial diseases, idiopathic pulmonary fibrosis (IPF), has escalated an interest in these diseases amongst professionals and in the general public. It was soon discovered that there was a lack of experts involved with these disorders amongst respiratory physicians, radiologists and pathologists. Thanks to the fact that there are still enthusiasts in the field of medicine who are attracted by the unexplored, and who

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_1

want to learn new things, a network of pneumological departments dealing with patients with ILD was formed. Furthermore, pneumologist began to search for enthusiast within their radiology and pathology counterparts to fulfil the philosophy of a multidisciplinary approach.

It is important to note that it is the radiological findings of diffuse pulmonary disease that are essential for directing us towards the correct diagnosis or being diagnostic in itself. However, for the radiological findings to be accurate and evaluated effectively, radiologist need intensive and long-term training, though it is appreciated that they have multiple other radiological interpretations to analyse other than the lungs or specifically ILD. Nevertheless, the most enthusiastic radiologists have learned the most and then taught us respiratory physicians in return as part of the multidisciplinary approach.

This book is structured and targeted to guide both radiologists and pneumologist. In the overview, it reveals the key in recognition and differential diagnosis when studying radiological findings of an ILD. Further, clinical-radiological cases demonstrate the role of a multidisciplinary approach, with an emphasis on the evaluation of radiological findings in practice.

2 The Role of Multidisciplinary Team in the Diagnosis and Differential Diagnosis of Interstitial Lung Disease

Martina Sterclova

Taking care of a patient with any chronic disease usually requires the collaboration of skilled physicians from different fields, at the beginning of the illness, during its course, and throughout the diagnostic process.

The role of the multidisciplinary team (MDT) has become particularly important with the discovery of new therapeutic options. In the beginning of this century, the treatment of practically all patients with ILD was based on systemic corticosteroid therapy and sometimes immunosuppressants. Over time it became clear that not everyone benefited from this approach. In some patients, this treatment significantly worsened their prognosis. Later, antifibrotic therapy became available for patients with idiopathic pulmonary fibrosis (IPF), sirolimus for lymphangioleiomyomatosis (LAM), and rituximab for selected patients with systemic connective tissue disease (SCTD) or with non-specific interstitial pneumonitis (NSIP). With advancing knowledge in immunology and transplant medicine, the number of patients for whom a lung transplant has become a treatment option is rising and it appears there is this trend even within the ILD group. One must note that there are differences in the optimal time when a patient should be referred as a potential candidate, and eventually signed as the definitive candidate for a lung transplant. Besides pharmacological treatment, non-pharmacological procedures including physiotherapy and the introduction of nutritional measures are also important, again with different levels of urgency according to the diagnosis and the overall condition of the patient.

Thus, it seems ILDs have moved from the role of 'Cinderella,' who creeps alongside her sisters, namely 'bronchial obstruction' and 'lung cancer,' to become the centre of interest to physicians, pharmaceutical companies, and even health insurers, who pay for the care of these patients.

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_2

ILDs are considerably heterogeneous group of disorders, and in recent years, the field has noted exceptional advances and changes, especially with the risen role of the MDT and consultations in the centres for diagnosis and treatment of ILDs.

2.1 Why Should the Diagnosis Be Determined by a Discussion Based of Doctors of Different Specialities?

Some research illustrates that the discussion of a patient's case led by doctors of different specialties may increase the likelihood of a diagnosis being determined correctly. Within some diagnostic debates, MDT participants can simply agree (an example is IPF, where it has been proven that the conformity between participants reaches the highest level), others can determine with a certain degree of probability, and some disease may remain as a differential diagnosis (such as chronic hypersensitivity pneumonitis, where for many patients, despite the use of all diagnostic methods and options, IPF 'stays in play').

One of the reasons why patients with ILD should be discussed within an MDT is due to a low level of agreement between radiologists that are not fully trained in pulmonology. For a pulmonologist who does not specialise in the care of patients with ILD, HRCT (high-resolution computed tomography) description is crucial, as this description may provide a definitive diagnosis. The MDT centres for patients in ILDs consider the results of all available examinations, and supplementary examinations may be recommended as the team's conclusion may influence the conclusion to histological findings. According to some research, the conclusions of MDT for ILD diagnosis are different in 33% of all cases from the conclusions of the referring pneumologist. In the case of IPF, the conclusions differed by up to 50%.

Determining the correct diagnosis often influences decision-making during the treatment process. Just as it is an error to treat patients with lymphangioleiomyomatosis with systemic corticosteroid therapy, treating IPF with combined immunosuppressive therapy may be fatal. Data available indicates that an MDT can not only modify the diagnostic conclusion for ILD but also can aid in differing treatment regimes, which is of significant benefit for patients, as it reduces the risk of iatrogenic damage.

The second benefit of an MDT is assessing the need for further investigations, i.e. whether a lung biopsy is indicated for the patient and balancing the risks versus benefits for safe and effective patient care. Some research indicates that up a third of patients, who are discussed within MDT, principally as potential candidates for a surgical lung biopsy, can be diagnosed without the insight of the histological findings. A surgical lung biopsy represents a higher risk of developing acute exacerbations for some patients. Higher risk groups include patients over 65 years of age and patients with severe lung function impairment. It is likely that an MDT discussion over a patient's case may reduce the need for invasive investigations without lowering the likelihood of reaching a correct diagnosis.

2.2 What Is the Optimal Structure of an MDT?

The structure is in the Czech Republic based on the tradition of an oncological MDT, the team involves the patient's primary physician, a specialist in the field (in the case of an oncological MDT a pneumo-oncologist, oncologist and radio-oncologist), radiologist and a thoracic surgeon. In the MDT dealing, members involved are: the patient's primary physician, an ILD specialist, radiologist, and thoracic surgeon. If the patient has undergone a lung biopsy, the attendance of a pathologist trained in the ILDs is favourable.

In some clinics, members of the MDT also involve rheumatologists, immunologists or transplant surgeons. In this respect, it is evident that no united standard has been created to define how many doctors or which expertise should form the MDT.

As a minimum requirement in the Czech Republic, members of the MDT can probably be considered the patient's primary physician, an ILD expert (a physician from the centre for the diagnosis and treatment of ILD) and a radiology expert in ILD.

2.3 What Is the Necessary Information to Be Presented to the MDT?

The extent to which the patients with ILD are examined differs between various centres. The cornerstone for diagnosis is made of patients history, physical examination, high-resolution computed tomography (HRCT) of the lung, lung function tests including transfer factor, bronchoscopy with bronchoalveolar lavage, and screening of systemic connective tissue diseases (usually in the form of an autoantibody panel scan available to the department). Some patients also undergo spiroergometry, echocardiography, rheumatological examinations, a 6-minute walk test (6MWT) or sleep monitoring.

From a practical point of view, it is important for the presenting general attending physician to know the outcome of the examinations the patient was subjected to. The presenting physician should be able to answer questions aimed at eliminating exogenous causes of the disease, involvement of systemic connective tissue disease, assessment of the severity of impaired lung function, to know the patient's co-morbidities and to know standing regarding the possibility of a lung biopsy. Further, it is important for the presenting physician to know the aims of their presentation (Table 2.1).

It is considered appropriate to prepare the case prior to the MDT meeting, and ensure a thoroughly investigated of the patient's documents so that the MDT members are presented with enough information necessary for when considering the differential diagnosis.

The primary physician also should have in mind the indication and purpose of the case presented and should aim to focus on what information it is specifically required to reach their aim through the MDT outcome. As a rule, the discussion of an oncological MDT concerns the treatment modalities suitable for a patient;

Table 2.1 Recommended range of information that the presenting doctor is expected to know during the MDT discussion

History: with a focus on the patient's co-morbidities, as well as smoking history and medication, and possible risks of exposure to/inhalation of organic/inorganic antigens
Current illness: with a focus on the patient's overall general condition and mobility, physical findings, non-respiratory issues (especially in patients with systemic connective tissue diseases, sarcoidosis, or LAM)
Blood tests: to note significant deviations in the standard blood count or biochemistry, autoantibody test results, eventually cellular/humoral immunodeficiency
Chest imaging (HRCT): when it was performed and what was the original assessment/ outcome
Lung function: including transfer factor
Bronchoscopy with bronchoalveolar lavage: the percentage of cells in the BAL, CD4+/CD8+, and eventually a TBB result, if available
Histological findings: the result of the surgical lung biopsy, cryobiopsy, and findings from material taken at EBUS

LAM lymphangioleiomyomatosis, *HRCT* high-resolution computed tomography, *BAL* bronchoalveolar lavage, *TBB* transbronchial biopsy, *EBUS* endobronchial ultrasound

however, MDT discussions involving ILD patients are globally more focused on the diagnosis. We believe that the potential for assessing a patient's case by a multidisciplinary approach reaches significantly beyond the diagnostic horizon, especially in the case of rare diseases, where the treatment requires an experienced team and access to medication.

Possible reasons for presenting a patient within the MDT

1. Determining the diagnosis—the patient's data is presenting with the aim to determine the diagnosis.
2. Determining the diagnosis after the completion of recommended examinations—i.e. during a previous MDT session, it may have been suggested to complete certain investigations (a patient's post-pulmonary biopsy is usually presented in this manner).
3. Determining the treatment process for a patient with a known diagnosis—especially if the health insurance reimbursement for the treatment is linked to a previous MDT discussion, or if it is a rare disease, or if the patient has been treated previously and a less common treatment is considered.
4. Discussion of an unusual course of illness in the patient with a pre-determined diagnosis, even with established treatment—considering the clinical course, eliminating possible complicating factors, possibly changing the diagnosis or changing the treatment.

2.4 What Should the MDT Meeting Record Contain?

Although the habits of various institutes differ, when it comes to MDT meeting records, it is advisable to record the date, names of the attending participants, by whom and the aims which the patient is presented for. It is also important to include

the name of the person who documented the record. With respect to the request made, the meeting should follow either a diagnostic approach or a recommendation for further examining or treatment.

2.5 How Often Should the MDT Meet?

There is no general valid recommendation as to how MDT meetings should take place. Usually, the frequency of the sessions depends on the number of patients requiring care. The presentation may involve either new patients to determine their diagnosis or a discussion regarding recommendations for further investigations, or patients who have undergone the entire diagnostic process according to previous recommendations and require a decision on the appropriate treatment. Also presented are patients with a known diagnosis, who are or have been treated and a change in treatment needs to be considered, or the course of the disease does not correspond to the original diagnosis. The MDT typically meets variably from several times a week to once a month and each meeting lasts for approximately one to three hours. How often an MDT meets also is influenced by the staff capacity of the particular clinic.

2.6 Is the Diagnosis Determined Based on a Discussion of Experts Accurate?

Recently published data shows that a change in the diagnosis follows in 33–53% of patients whose case is discussed within an MDT specialising in ILD. Furthermore, in 71% of patients whose disease is assessed as unclassifiable prior to an MDT discussion, leave with a diagnosis and specific treatment recommendation.

There is no data available to demonstrate that the discussion of an ILD patient case within an MDT leads to prolonging or improving the quality of life. Nevertheless, there are similar cancer patient studies, demonstrating that not only a discussion within an MDT influence their survival (mainly due to the choice of treatment), but also it reduces the costs associated with the treatments (as only patients who are more likely to have a proven benefit are treated).

Model of MDT in the United Kingdom is very inspirative - MDT members must have appropriate qualification. These qualifications are clearly defined, and the team members must prove at regular intervals that they are competent to meet the conditions. Amongst other things, the form and content of MDT outcome report are monitored.

2.7 What Are the Pitfalls of MDT Debates and What Usually Determines the Outcome?

Factors that are clearly involved in the effectiveness of MDT decision-making include good team management and a clear definition of the goals which the case discussion is targeted to reach. According to some studies, a warm atmosphere and

a unified team opinion on recommended procedures and investigations play a role. Interestingly, the data concerning the decision-making of MDT meetings in the UK (generally in MDT meetings regarding patients with chronic diseases) show that 'less sometimes means more.' In numerous cases, it has been suggested that smaller teams decide more effectively, especially with teams of contributing doctors from differing expertise.

Less efficient teams involve too many experts, as communication barriers can evolve as not all participants have the same level of knowledge and skills. It then becomes unclear as to who has which role and responsibility. If the MDT includes a large group of doctors of many specialties, it is absolutely necessary that team leadership is entrusted to one member who is the most experienced, and the objectives of the meeting have been clearly defined in advance.

Note

If the MDT is to decide on the patient's fate, it is essential that the case must be discussed by experts with experience in the particular field. The presenting doctor should know the patient's history and examination reports in detail, and know their aims and expectations of the MDT outcome. A written record should always be made from the MDT meetings and entered in the patient's notes. Patients with a complicated or unusual diagnosis may require repeated consultations within an MDT.

Further Reading

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Pneumological Basics of Differential Diagnostics of ILD

3

Martina Sterclova

Although the lung interstitium may be affected by a variety of factors, the differential diagnosis of ILD is not as difficult as many believe. For the clinician, it is important to exclude idiopathic ILD from those with a known aetiology, and to decide how to proceed with the treatment. Although there are many diseases affecting the lung interstitium, there is a specific treatment for a small group of patients. However, in some patients, treatment cannot be offered regardless of a known aetiology, whereas another group of patients may be candidates for immunosuppressive therapy.

3.1 What Is the Basis for Determining an ILD Diagnosis?

Thorough patient history, including the patient's past medical history, long-term medications, smoking history, their occupation/hobbies/environmental exposure risks, or family history of lung disease is essential. Patient's medical history is crucial and cannot be omitted, as it is based on which we are able to focus attention towards establishing the correct diagnosis. It is important to note the reason for referral, the presenting complaints and type of examinations which were already performed. Although modern modes of examination are available, a face-to-face detailed patient interview remains an irreplaceable building block for clinicians.

A complete physical examination including auscultation must be performed, as an interstitial lung disorder may be a manifestation of a systemic disease. The patient's overall clinical state may limit the number and type of examinations we plan to perform, and eventually treatment options. Symptoms may be a manifestation of more than one illness. Initially, a chest X-ray in two projections and pulmonary function tests including the diffusing capacity is performed. Based on the

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_3

patient history and clinical examination, a complete serology including autoantibody screening is requested. Lung HRCT is performed in all patients suspected of having an ILD. If patient's clinical status allows, bronchoscopy with bronchoalveolar lavage, and possibly with a transbronchial lung biopsy, is performed. If the above-mentioned examinations are still unable to confirm a diagnosis, then the patient may qualify for a more invasive but better yielding methods of pulmonary biopsy. Although not widely accessible, cryobiopsy and/or biopsies navigated by endobronchial ultrasound (when samples from specific lymph nodes are needed) are performed, and in selected cases, a surgical pulmonary biopsy may be required.

The diagnosis of ILD is not a matter of one single examination. It is based on the integration of the obtained results, information, and findings. The consensus on a specific diagnosis should be handled by an experienced team, to avoid missing the rare types of ILD. Different disease states may present with similar radiological and histopathological patterns; therefore, the final diagnosis should be made by a pneumologist in cooperation with an MDT.

3.2 How Are ILD Classified?

The basic way to classify ILD is by grouping according to known aetiology, idiopathic, granulomatous ILD and rare ILD (Tables 3.1 and 3.2). There is, of course, a possible partial overlap between the groups. However, other aspects can be considered when classifying ILD, for example, the rate of occurrence of symptoms (acute, subacute or chronic) or treatment options.

Table 3.1 Classification of ILD according to aetiology

ILD of known aetiology
ILD caused by inhalation of dust, vapours, and gases of inorganic material
ILD induced by medication
ILD of infectious aetiology: bacterial, fungal, viral, or protozoal
ILD caused by radiation
ILD of cancerous descent: tumorous lymphangitis, and primary diffuse pulmonary tumours
ILD caused by systemically acting toxic substances, e.g. paraquat
Transplant reaction, rejection, and graft versus host reaction
ILD associated with diseases of other organs: hepatitis, liver cirrhosis, left heart failure, chronic uraemia, and idiopathic intestinal inflammation
ILD caused by smoking
ILD of unknown aetiology
Idiopathic interstitial pneumonia
Sarcoidosis
ILD within systemic connective tissue disease
ILD within vasculitis
Eosinophilic pneumonia
Pulmonary Langerhans cell histiocytosis
Hereditary and familial ILD, e.g. tuberous sclerosis
ILD associated with storage disorders: amyloidosis, and alveolar proteinosis

Table 3.2 Revised classification of idiopathic interstitial pneumonia of the American Thoracic Society (ATS) and European Respiratory Society (ERS): multidisciplinary diagnostics

Common idiopathic interstitial pneumonia
Idiopathic pulmonary fibrosis
Idiopathic non-specific interstitial pneumonia
Respiratory bronchiolitis with an interstitial lung disease
Deliberative interstitial pneumonia
Cryptogenic organising pneumonia
Acute interstitial pneumonia
Rare idiopathic interstitial pneumonia
Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonia[a]

[a]Causes of unclassifiable idiopathic interstitial pneumonia: (1) inadequate clinical, radiological or pathological data/results, (2) major discrepancies between clinical, radiological and pathological findings due to the following: (a) previous treatment affecting subsequent radiological or histopathological findings, (b) a new subunit or an unusual variant of an already known subunit according to the current ATS/ERS classification, (c) multiple HRCT and histopathological types in one patient

3.3 Can the Prognosis of the Patient Be Affected by a Well/Poorly Determined Diagnosis?

Early this century, an accurate diagnosis had no greater impact on the treatment of choice for patients with ILD, and often did not affect the prognosis. For patients with a history of possible agent-induced exposure (most commonly either patients with pneumoconiosis, where the association between exposure and disease is apparent and known for a long time, or patients with hypersensitivity pneumonitis), exposure is limited (or recommendation are made to do so). In the other cases, systemic corticosteroid therapy, possibly in combination with immunosuppressant, was considered.

Although IPP treatment in some cases does not differ from the above-mentioned example, some patients may be directly endangered by anti-inflammatory therapy. Specific treatment exists not only for patients with idiopathic pulmonary fibrosis (antifibrotics) but also for patients with lymphangioleiomyomatosis (sirolimus) or alveolar proteinosis (granulocytes stimulating growth factor, or bronchoalveolar lavage). New therapies, especially biological therapy, also apply to patients with SCTD, including vasculitis. Unfortunately, currently, they lack the research to demonstrate the effects of these preparations on an isolated or dominant lung disorder. When treating SCTD with novel therapies, serious side effects resulting in diffuse parenchymal lung disease may occur and interfere with the differential diagnosis of SCTD. Neglecting possible drug-induced lung damage or infectious complications may be fatal.

Treatment with TNFα blockers in patients with rheumatic disease increases the risk of developing tuberculosis, and cyclophosphamide increases the risk of developing pneumococcal pneumonia (immunosuppressants generally increase the risk of infections by opportunistic pathogens). Long-term treatment with immunosuppressants increases the risk of developing cancer and may manifest in the lungs.

It is a grave error and of harm to the patient to not consider all available treatment options and only think of ILDs as "corticosteroids yes or no."

3.4 Does Every ILD Have Its Specific Image?

The human body responds to any injury with a limited number of responses. Clinical manifestations of ILD are identical with those of respiratory disease, i.e. coughing or exertional dyspnoea that is either isolated or occasionally associated with systemic symptoms (fever, weight loss, and fatigue), or additional organ involvement (particularly with SCTD). Radiologically (and even histopathologically) ILD binds to the "patterns" of damage where a radiological pattern can classify different types of an ILD. It may be so that only the probability with which we can meet a pattern of damage is different. "Patterns" can also be combined, and this combination may be indicative of a specific ILD. When considering these specific patterns manifested by the lung injury, we may determine the classification of ILD with a high probability.

3.5 Who Diagnoses ILD?

The diagnosis of ILD is determined by the respiratory physician. However, it is necessary for the diagnostic reasoning to consider clinical and laboratory findings, and the HRCT upon consultation with an expert radiologist. The respiratory physician with all the necessary patient information, and together with the radiologist (and in some cases the pathologist), combine individual fragments of data towards the patient's diagnosis. It should be noted that upon review, the diagnosis may change according to the clinical development of the disease.

Note
The diagnosis of ILD cannot be determined based on the result of one examination (neither solely on chest HRCT). A poorly determined diagnosis may lead to fatal consequences for the patient. The radiologist should distinguish the "patterns" of the disease and their association with the individual types of ILD, and the conclusion of the HRCT description should include the differential diagnosis of the "patterns" captured.

Radiographic Anatomy

4

Eva Kocova

The pulmonary interstitium can be considered as an interfused tissue, which consists of a supportive connective tissue network of varying density, lymphatic vessels, blood vessels (with capillary microstructure) and tissue fluid. To understand the arrangement of the pulmonary interstitium, anatomical knowledge of the secondary pulmonary lobule is necessary. The secondary pulmonary lobule is the basic functional unit of the lung tissue, which is peripherally bound by a connective tissue septa containing lymphatics and small pulmonary veins. It is ventilated by a secondary pulmonary bronchiole and blood supply is provided by a secondary pulmonary arteriole, which together enters the lobule centrally and then branch out together. On cross-sectional imaging, the secondary pulmonary lobule has a polygonal shape, and its size usually ranges from 10 mm to 25 mm. Each lobule contains further subunits called pulmonary acini, which are supplied by the terminal bronchioles and arterioles, ventilated by the respiratory bronchiole, forming the primary pulmonary lobules [1, 2].

The pulmonary interstitium consists of three interconnecting compartments of connective tissue. The first is microinterstitium within the alveolar wall, where tissue fluid is formed. The second zone is the peripheral interstitium, formed by the wall of the secondary lobule. This thin connective tissue contains a collection of lymphatic cells and pulmonary veins, which penetrate the lung tissue towards the hilum, independently of the bronchoarterial bundle. If the secondary lobule is located peripherally, a section of its wall is formed by a space under the visceral pleura (subpleural space). The third zone is the central (axial) interstitium, formed of sparse connective tissue which surrounds the bronchoarterial structures (the bronchovascular bundle). The lymphatic vessels running towards the pulmonary hilum are present in the central peribronchoarterial space. They are connected at

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_4

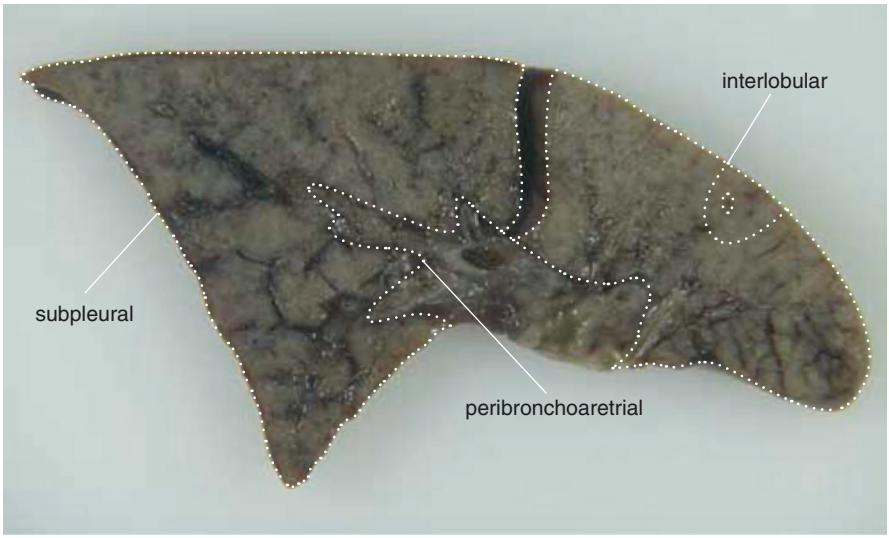

Fig. 4.1 Pulmonary interstitium—picture kindly loaned from Helena Hornychova, MD, PhD (The Fingerland's Department of Pathology, University Hospital Hradec Králové)

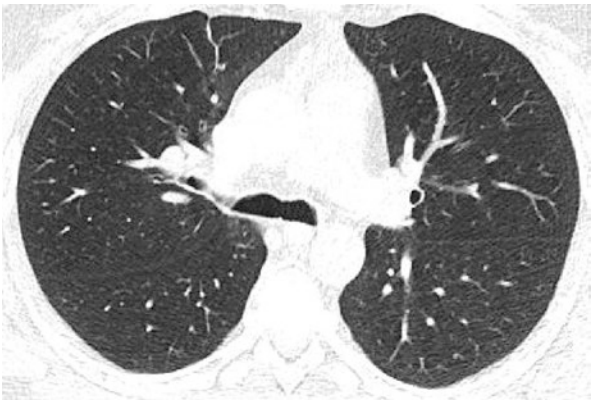

Fig. 4.2 HRCT of the lungs, transversal reconstruction: a normal pulmonary interstitium, subpleurally it is without apparent bronchi and interlobular septa

outlets of arteries and bronchi from the secondary lobules. This zone begins in the centre of the lobules and terminates in the pulmonary hilum, creating the main pathway for draining tissue fluid from the lungs [1, 2] (Fig. 4.1).

On lung HRCT of healthy individuals, the interlobular septa are not apparent. Sometimes, they may be scarcely visible, but are not dense. The centrilobular bronchovascular bundle gradually narrows as the distance from pulmonary hilum increases. In healthy individuals on HRCT, in the peripheral subpleural part of the lungs, only sparse vascular structures centrilobularly can be differentiated (with no apparent bronchi or borders of secondary pulmonary lobules) (Fig. 4.2).

Depending on the location of lesions within the secondary pulmonary lobule, we distinguish them as centrilobular, panlobular, perilymphatic, random and

interlobular. The correct identification of the pathological finding within the secondary lobule is crucial in the differential diagnosis of lung diseases.

Centrilobular pathological findings are in the central part of the secondary pulmonary lobule—they occur in diseases primarily affecting centrilobular structures, i.e. arteries, bronchi, lymphatic vessels, and the central interstitium. Generally, the centrilobular lesions are not in contact with the wall of the secondary pulmonary lobule. If the centrilobular patterns are large enough, they may reach the boundaries of the secondary pulmonary lobule (known as panlobular).

For diagnostic purposes, the simplest method is the identification of the interlobar fissures, as they are spared by these patterns—the so-called bare areas. This is as the centrilobular pathological findings are in the central part of the secondary pulmonary lobule, are not in contact with its walls, and thus it cannot affect the interlobar fissures. Due to the almost constant size of the lobules, these patterns are uniformly spaced apart. Centrilobular patterns include nodules—solid or sub-solid (centrilobular ground glass opacities—GGO), tree in bud, regions of hypodensities, and pathological bronchial processes (Figs. 4.3 and 4.4).

Perilymphatic distribution means the lung is afflicted in places where lymphatic vessels are located—in the central part of the secondary pulmonary lobule, including the interlobular septa, and subpleural region. On HRCT of the lungs, the findings are evident as a thickening of the central or peripheral pulmonary interstitium: **smooth** (forming reticulations, and bronchial wall thickening), **nodular** (perilymphatic nodules), or **reticulonodular** (a combination of thickening of the interlobular septa or a thickened bronchial wall with nodules). The nodular involved in perilymphatic distribution is formed of sharply demarcated nodules with soft tissue densities, often in clusters. The simplest identification of the perilymphatic distribution of nodularities is the assessment of the interlobar fissures—if the pathological finding is located on the interlobar fissure, it rules out centrilobular pathology, but can be either perilymphatic or random distribution (Fig. 4.5).

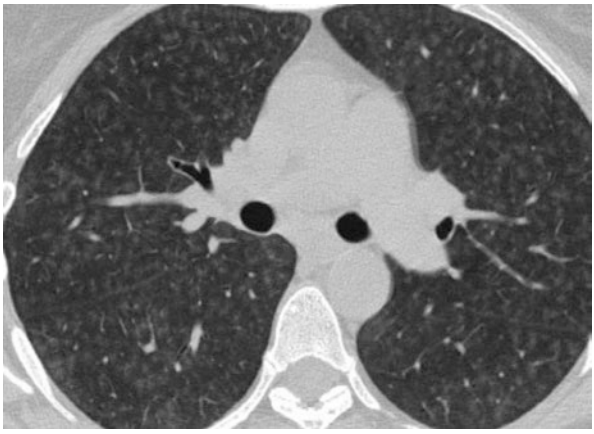

Fig. 4.3 HRCT of the lungs: multiple fine centrilobular sub-solid nodules (GGO). The interlobar fissures are not affected—bare areas

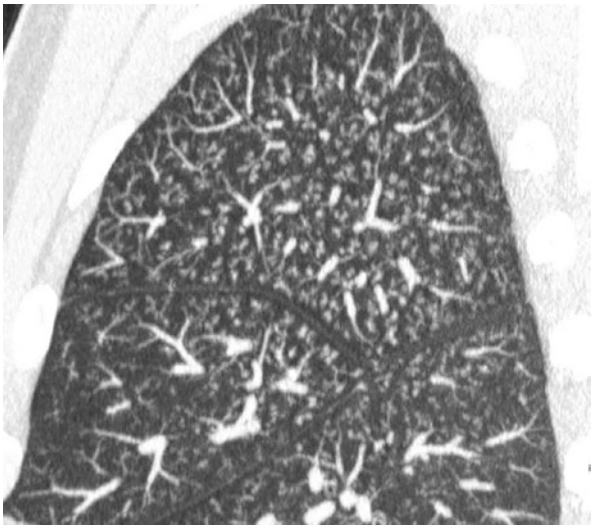

Fig. 4.4 HRCT of the lungs, sagittal reconstruction: centrilobular tree-in-bud patterns, with interlobar fissures without apparent nodules

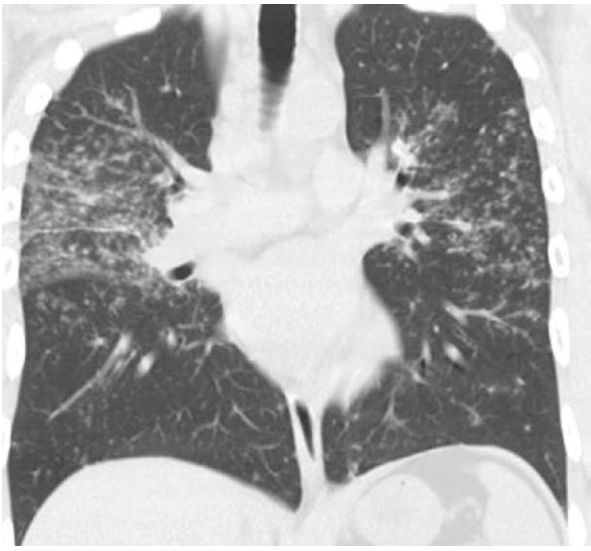

Fig. 4.5 HRCT of the lungs, coronal reconstruction: multiple nodular patterns in the perilymphatic distribution (nodules in the central part of secondary pulmonary lobules and multiple nodules on the interlobular fissure, and in the subpleural areas, arranged in clusters)

In cases where the pathological process does not completely respect the structure of the secondary pulmonary lobule, being located randomly and almost uniformly in the lungs, it is a **random distribution** (Fig. 4.6).

Interlobular pathology affects supporting connective tissue, pathological conditions of the perilymphatic or venous system. On the HRCT imaging, this is displayed as **linear opacities**.

How do we distinguish the location of these nodularities within the secondary pulmonary lobule?

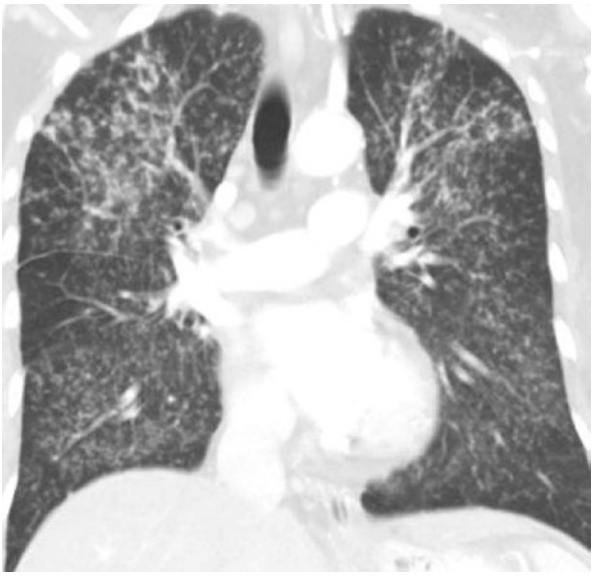

Fig. 4.6 HRCT of the lungs, coronal reconstruction: multiple nodular pathology patterns in a random distribution

We look at the interlobar fissures—are they smooth?

- Yes—it is centrilobular distribution
- No—the distribution is perilymphatic, or random

Interlobar fissure contains nodules—how to distinguish between perilymphatic and random distribution?

Do the nodules prevail within the subpleural and peribronchovascular region?

- Yes—it is a perilymphatic distribution (nodules are usually organised in clusters)
- No—it is a random distribution (nodules are almost uniform in the lungs)

4.1 Location of Radiological Changes

The radiodiagnostics of lung lesions continues with **localising the pathological findings within the whole lungs**—are the pathological processes typically located in the apex or the bases of the lungs, in the periphery or the central part of the lungs?

Upper pulmonary lobes involvement prevails in all chronic ventilatory pulmonary disorders—smoking-related lung diseases, silicosis, pneumoconiosis, hypersensitivity pneumonitis (HP), sarcoidosis, tuberculosis, with the only exception being asbestosis.

Lower pulmonary lobes are affected by aspirations, an ILD of a usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), cryptogenic organising pneumonia (COP), pulmonary oedema, alveolar haemorrhage, etc.

A **diffuse** pulmonary disorder can be seen in carcinomatous lymphangiopathy or EAA.

Pathological processes with the predilection to **central lung zones** are pulmonary oedema, sarcoidosis, pneumoconiosis, alveolar proteinosis, and carcinomatous lymphangiopathy.

The **periphery** is typically affected by UIP, non-specific interstitial pneumonia, acute interstitial pneumonia, cryptogenic organising pneumonia, desquamative interstitial pneumonia, etc.

4.2 Radiological Basics

The diagnostic approach to ILDs begins with the assessment of the **posteroanterior and lateral chest X-ray**. When an interstitial lung disease is suspected, the basis of diagnosis lies in the exclusion of the presence of other unexpected pathologies. Lung volume assessment is also necessary. Changes in the lung volume may be the first step in the differential diagnosis of a pulmonary pathology (pulmonary hyperinflation occurs typically with asthma or pulmonary emphysema, and decreased lung volume is a sign of pulmonary fibrosis or atelectasis).

In a plain chest X-ray, an interstitial disorder may manifest as a localised or diffuse increased reticulation, pathological translucence or consolidations.

High-resolution computed tomography (HRCT) should be ordered if chest X-ray shows clear signs of interstitial lung disease, or chest X-ray is normal but clinical suspicions prevail. HRCT is the only imaging method that allows a detailed view of the pulmonary interstitium. Its implementation should be indicated when any pulmonary interstitial disorder is suspected.

Computed tomography of the lungs is nowadays carried out almost exclusively by a spiral technique, in full inspiratory position, on the back with the upper limbs held behind the head. When indicated, it may be repeated in the same position at expiration (often performed sequentially to achieve the smallest radiation dose). Sometimes, to reveal pathologies in the dependent zones, the scan may also be repeated in the position on the abdomen.

The obtained data is then reconstructed in soft tissue and lung window. When examining the pulmonary interstitium, reconstructions are performed with a standard slice thickness with a maximum slice thickness of 2 mm (ideally 0.6–1 mm). These ultra-fine HRCT reconstructions performed by a "sharp" reconstruction algorithm allow us to give a detailed assessment of the structures of the secondary pulmonary lobule [1, 2].

Scans spreading over 2 mm cannot be considered as HRCT reconstructions and the interstitium not be assessed based on these scans.

4.3 Principles of Radiodiagnostics in Interstitial Lung Disease

- We look at the simple chest X-ray:
  - Is a pathological process present?
  - Has the lung volume changed?
- If we suspect a diseased pulmonary interstitium, we then implement HRCT of the lungs.
- Examining lung HRCT:
  - What is the dominant pattern?
  - Are there signs of fibrosis present? (A reduced lung volume, traction bronchiectasis, or honeycombing)?
  - Search where the pathological process is in relation to the anatomy—is the pathological process in the lungs diffuse? Predominance in the upper or lower lobes? Dominant in central or peripheral parts of the lung?
  - The presence of the pathological process is within the secondary pulmonary lobule—centrilobular, perilymphatic, or random?
  - Are there any other CT findings (lymphadenopathy, fluidothorax, fluidopericardium, skeletal involvement, adrenal enlargement, focal liver disease, etc.)?
- Consult clinicians regarding exposures, medication, the patient's past medical history, etc.

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HRCT Patterns

5

Eva Kocova, Filip Ctvrtlik, and Jana Votrubova

5.1 Decreasing Density

Eva Kocova

Under normal circumstances the pulmonary parenchyma on HRCT has a density ranging from −700 (750) to −920 (950) Hounsfield Units (HU). A decrease in HRCT density on below −920, or −950 HU, is considered pathological. It is caused by pathologies leading to a decrease of density or by cystic formations. They arise from traction, pathological widening of bronchial walls, focal hyperinflation, or by increased endoluminal bronchial pressure. Pulmonary emphysema is divided into centrilobular, panlobular or paraseptal, according to the location of the pathology in relation to the anatomy of the secondary pulmonary lobule. Centrilobular pulmonary emphysema is most commonly associated with chronic obstructive pulmonary disease (COPD) (Fig. 5.1).

Panlobular pulmonary emphysema is associated with α_1-antitrypsin deficiency. This emphysema is more homogeneous and affects the entire secondary lobule (Fig. 5.2).

Emphysematous changes affecting the subpleural region of the lungs constitute paraseptal emphysema. A variant of paraseptal emphysema is bullous emphysema, where the destroyed parts are connected into cystic formations larger than 1 cm (Fig. 5.3).

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_5

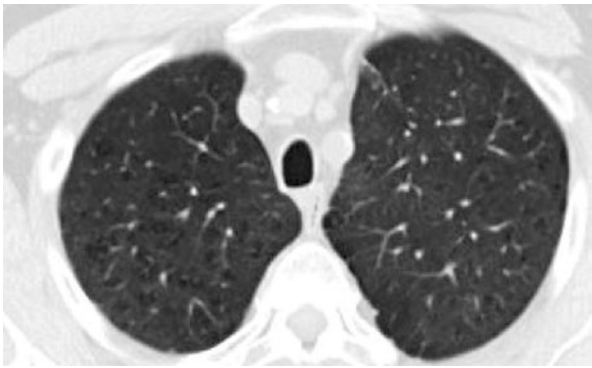

Fig. 5.1 HRCT of the lungs: centrilobular pulmonary emphysema

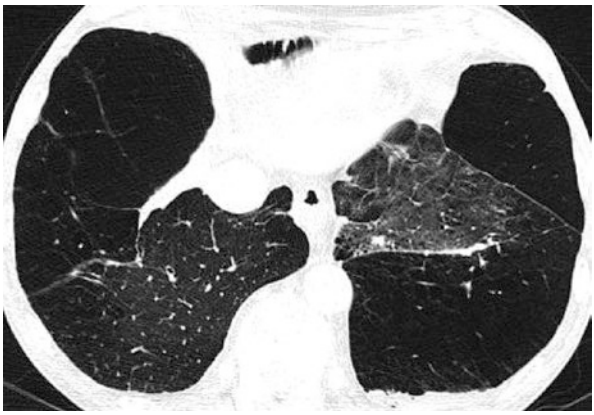

Fig. 5.2 HRCT of the lungs: panlobular pulmonary emphysema

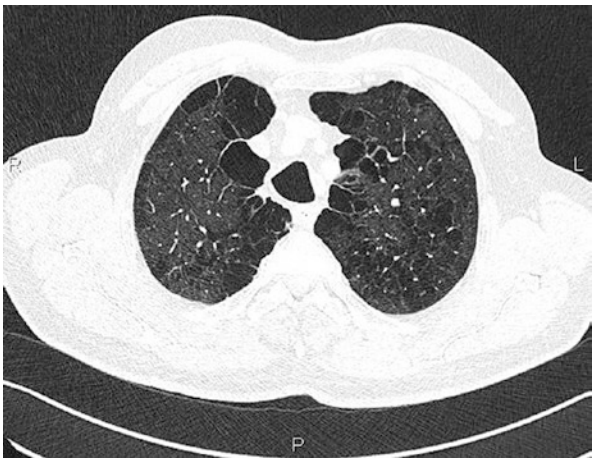

Fig. 5.3 HRCT of the lungs: paraseptal, bullous emphysema in combination with centrilobular emphysema

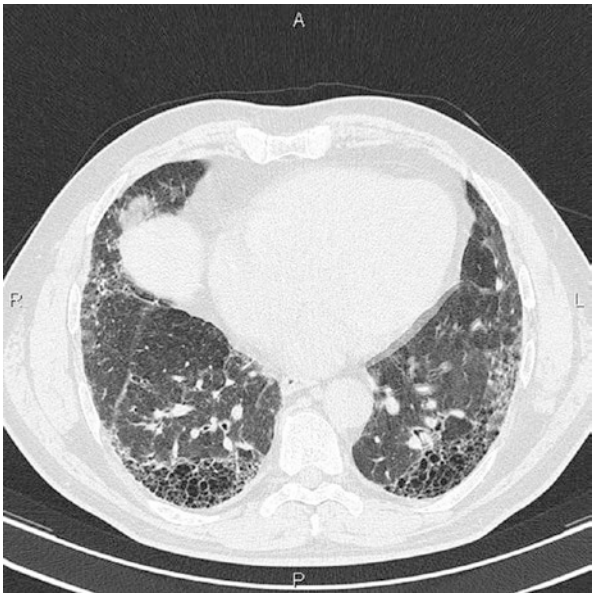

Fig. 5.4 HRCT of the lungs: UIP—the sign of honeycombing, distorsion of lung parenchyma and a reduction of volume of both lower lung lobes (interlobar fissure shift)

Honeycombing represents the destruction of the pulmonary parenchyma in advanced stage of pulmonary fibrosis. It is characterised by subpleural cystic structures with a thin wall, organised in one or several rows above each other. Other features of pulmonary fibrosis include a reduction in lung volume and the presence of traction bronchiectasis. The honeycombing typically occurs in UIP, asbestosis and in collagenosis with UIP patterns, etc. (Fig. 5.4).

Cysts in the lung parenchyma are "holes" with or without a clearly defined wall. Cystic pathological findings include pulmonary emphysema, honeycombing, and cysts. Sometimes cystic formations are also a feature of bronchiectasis if bronchiectasis is scanned transversally. The differential diagnosis of cystic lung diseases includes lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis (PLCH), lymphocytic interstitial pneumonia, cystic metastases or septic emboli, infectious pneumococcus, and rarely laryngotracheal papillomatosis or Birt-Hogg-Dubé syndrome (Fig. 5.5).

Bronchiectasis refers to irreversibly dilated bronchi that have a clear continuity with the bronchial tree. If it is encountered on a single CT scan, it may be impossible to differentiate a cyst from bronchiectasis. Therefore, for the differential diagnosis of bronchiectasis, it is necessary to revise the entire HRCT of the lungs continuously (Figs. 5.6 and 5.7).

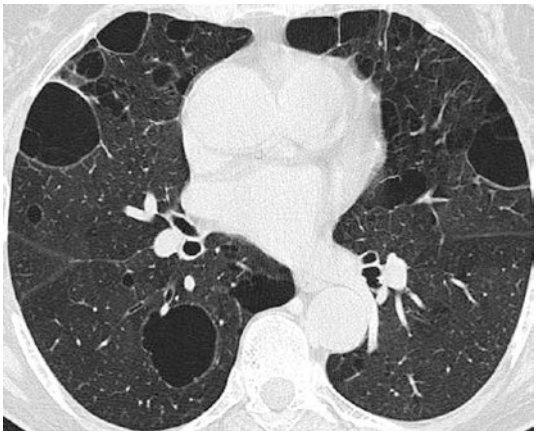

Fig. 5.5 HRCT of the lungs, transversal scan: cystic formations of pulmonary parenchyma with regular thin walls, located perivascularly and subpleurally in lymphocytic interstitial pneumonia

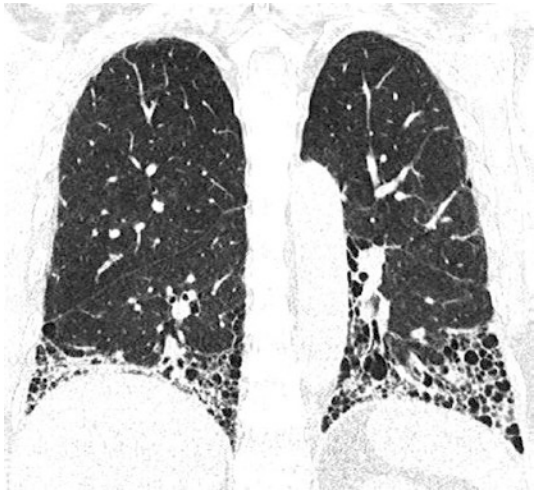

Fig. 5.6 HRCT of the lungs, coronal reconstruction: traction bronchiectasis in the lower lobes, honeycombing

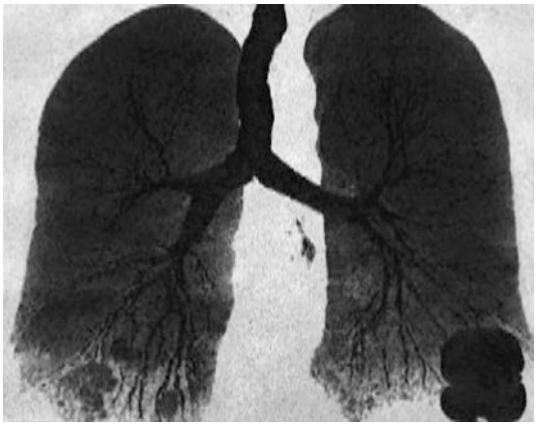

Fig. 5.7 HRCT of the lungs, MinIP reconstruction: traction bronchiectasis especially in the lower lobes

5.2 Linear Opacities

Eva Kocova

Linear opacities arise based on **thickening of the pulmonary interstitium**. They may be caused by the pathological enhancement of supporting connective tissue, lymphatic vessels, and the small pulmonary veins. This may be due to fibrosis, the presence of fluid or cellular infiltration, lymphatic thickening or pathological content in the distal alveolar spaces. These linearities are visible if they are aligned transversally to the CT scan. For their identification, it is advantageous to examine the pulmonary parenchyma in all three planes (transversal, coronal, sagittal). The interconnecting linear opacities form a network known as **reticulation**.

Linear opacities occur in pulmonary oedema, acute respiratory distress syndrome in adults (ARDS), UIP, non-specific interstitial pneumonia (NSIP), acute interstitial pneumonia (AIP), organising pneumonia, alveolar haemorrhage, and pulmonary storage disorders. They also occur in some cases of atypical infectious pneumonia or alveolar proteinosis.

They manifest in the form of the **thickening of interlobular septa** or **honeycombing.**

The thickened **interlobular septa** may be smooth, irregular or nodular. Smooth reticulations are typical for pulmonary oedema, lymphoma, and alveolar proteinosis. The irregular picture occurs in sarcoidosis, carcinomatous lymphangiopathy, lymphoma or silicosis.

Honeycombing is a sign of end-stage pulmonary fibrosis. It is represented by subpleural cystic structures observed in one or several rows, fibrotic thickening of the interlobular septa, and the collapse of the peripheral parts of acini, and with the destruction of central parts of the secondary pulmonary lobule. Honeycombing is typical (not pathognomic) for UIP (Table 5.1, Figs. 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15 and 5.16).

Table 5.1 HRCT criteria for usual interstitial pneumonia (UIP) (Figs. 5.8–5.16)

Typical image UIP (all 4 criteria)	Possible UIP (all 3 criteria)	The image does not correspond with UIP (any of the 7 criteria)
Maximum changes are subpleural and basal	Maximum changes are subpleural and basal	Maximum changes in upper and middle fields the dominant changes are peribronchovascular
Reticulation	Reticulation	Extensive GGO (dominance over reticulations)
Honeycombing with or without bronchiectasis	The absence of changes not corresponding with UIP (see third col.)	Extensive micronodular (bilaterally with upper fields dominance) discrete cysts (multiple, bilateral, outside honeycomb reconstruction region)
The absence of changes not corresponding with UIP (see third col.)		Diffuse image of mosaic perfusion/air trapping (bilaterally, in three or more lobes) consolidation in bronchopulmonary segments (lobes)

GGO ground glass opacities. According to Vašáková M, Šterclová M. Idiopathic pulmonary fibrosis—recommended procedure for diagnosis, treatment, and monitoring. www.pneumologie.cz

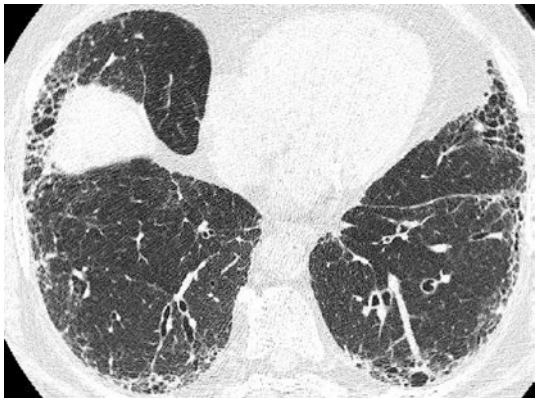

Fig. 5.8 HRCT of the lungs: patterns of typical UIP—reticulations in subpleural space, traction bronchiectasis, honeycombing

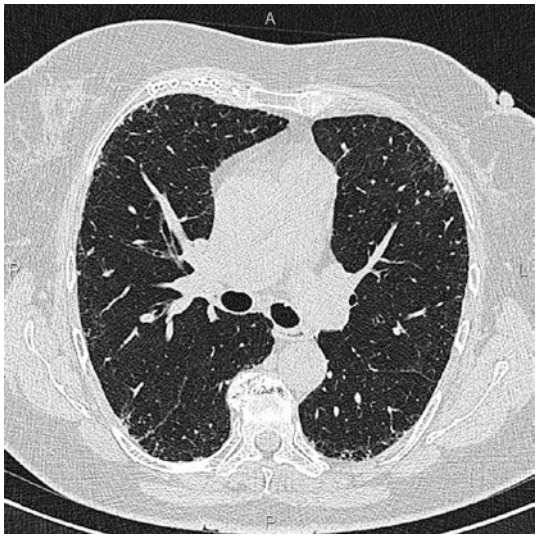

Fig. 5.9 HRCT of the lungs: signs of possible UIP—subpleural reticulations

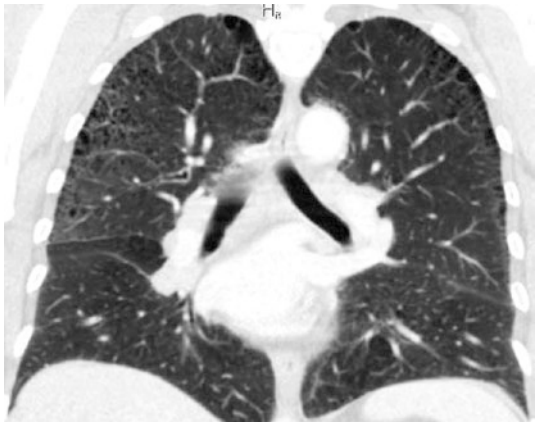

Fig. 5.10 Changes not corresponding with UIP: maximum changes in upper and middle lung fields (e.g. centrilobular emphysema)

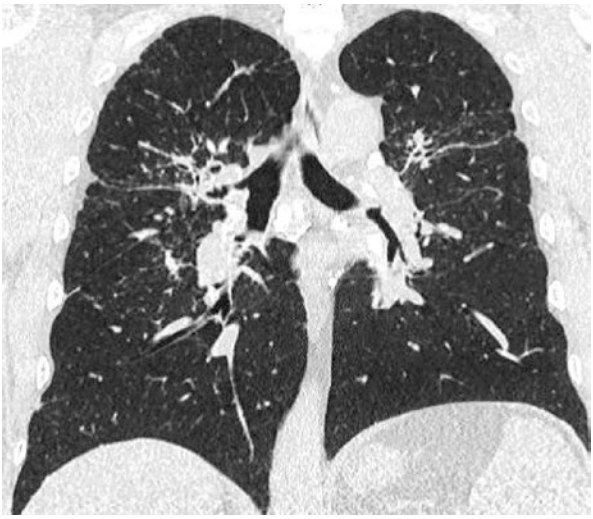

Fig. 5.11 Changes not corresponding with UIP: dominant changes peribronchovascularly (e.g. sarcoidosis)

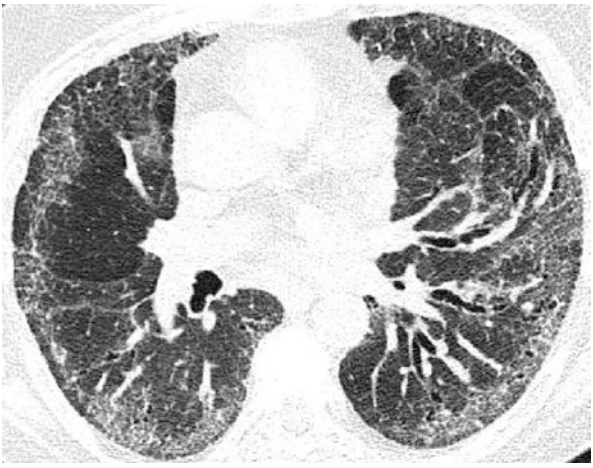

Fig. 5.12 Changes not corresponding with UIP: extensive reticulations and GGO (e.g. NSIP)

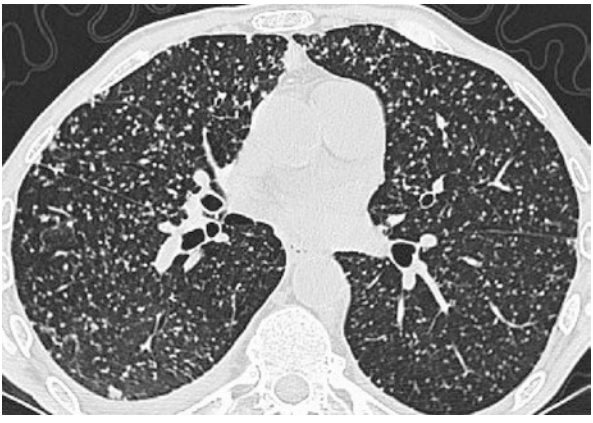

Fig. 5.13 Changes not corresponding with UIP: extensive micronodulations (e.g. miliary TB)

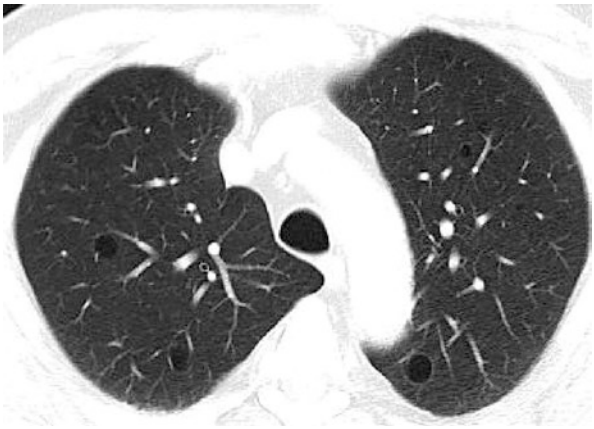

Fig. 5.14 Changes not corresponding with UIP: multiple cysts perivascularly (e.g. lymphocytic interstitial pneumonia)

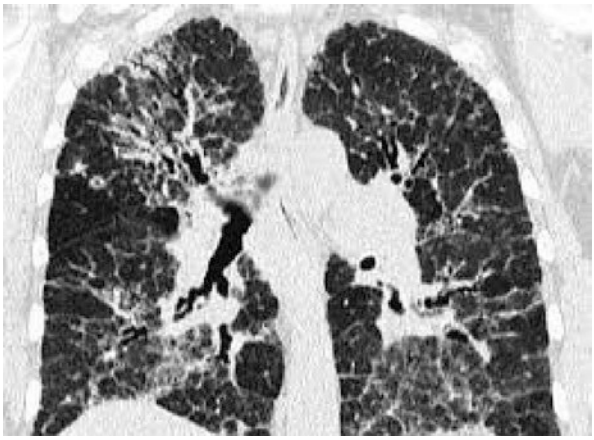

Fig. 5.15 Changes not corresponding with UIP: diffuse mosaic attenuation (e.g. chronic hypersensitivity pneumonitis)

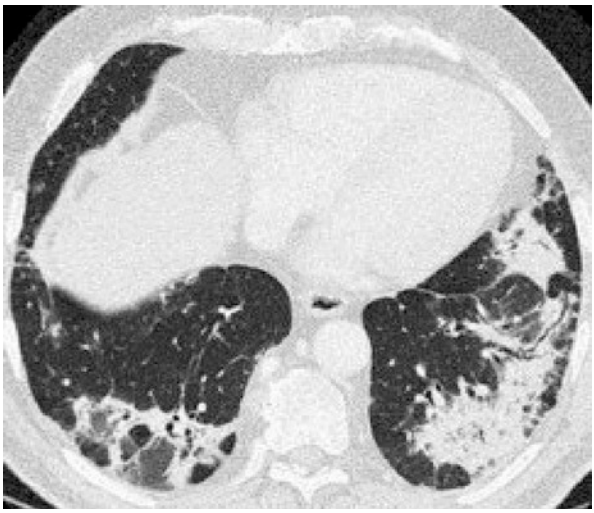

Fig. 5.16 Changes not corresponding with UIP: consolidation (e.g. organising pneumonia)

5.3 Nodulations

Filip Ctvrtlik

Nodules are assessed in size, appearance, density and craniocaudal distribution, and their distribution in relation to the secondary lobule, which may be considered as most important.

Distribution types:

1. Perilymphatic
2. Centrilobular
3. Random

The first step in the differentiation between these groups is to observe the pleura. The presence of nodules on the pleura (including the interlobar fissures) occurs in perilymphatic and random distribution types. In centrilobular distribution, nodules are not present on the pleura.

5.3.1 Perilymphatic Distribution

Perilymphatic distribution (Figs. 5.17, 5.18, 5.19, 5.20 and 5.21, Table 5.2) corresponds to the course of the lymphatic vessels in the lung. The nodules are therefore located peribronchovascularly, subpleurally, on the interlobular septa and centrilobularly. Subpleural nodules are best visible on fissures. The distribution throughout the lungs tends to be uneven, and nodules appear in clusters. Sarcoidosis is a typical representative.

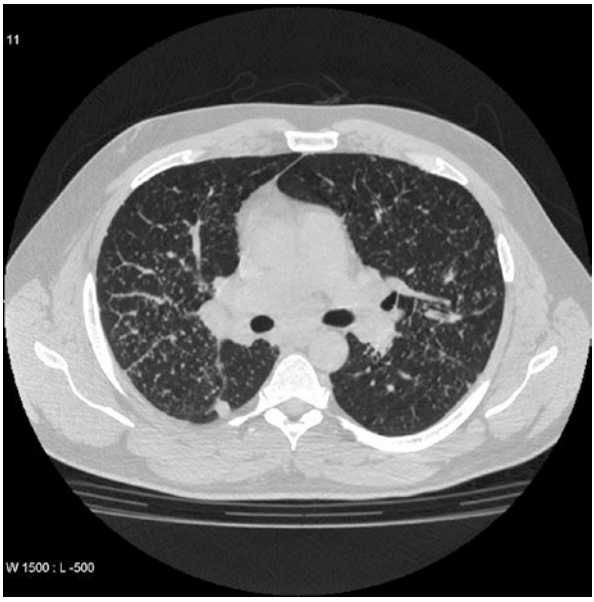

Fig. 5.17 Sarcoidosis—perilymphatic distribution of nodules

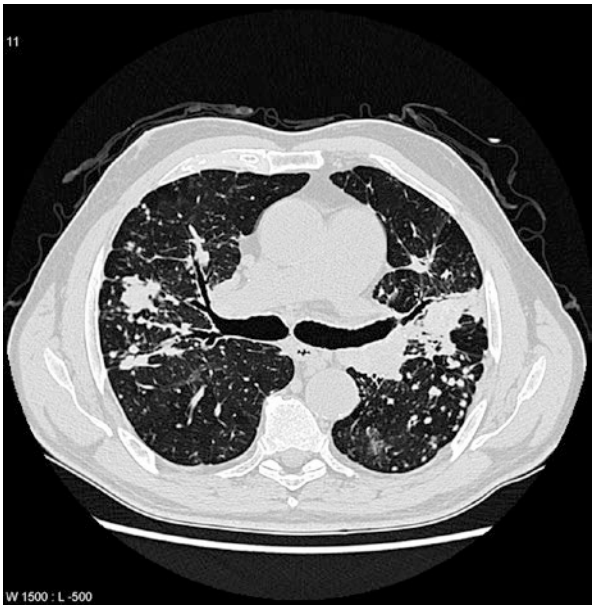

Fig. 5.18 Silicosis—perilymphatic distribution of nodules

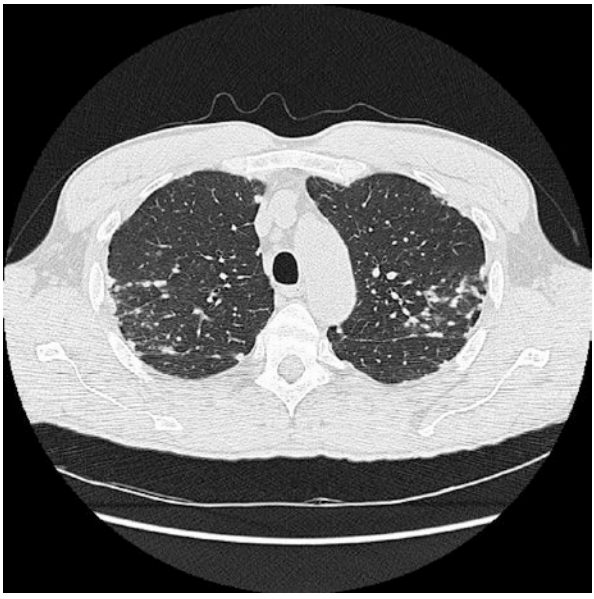

Fig. 5.19 Coalworker's pneumoconiosis—perilymphatic distribution of nodules

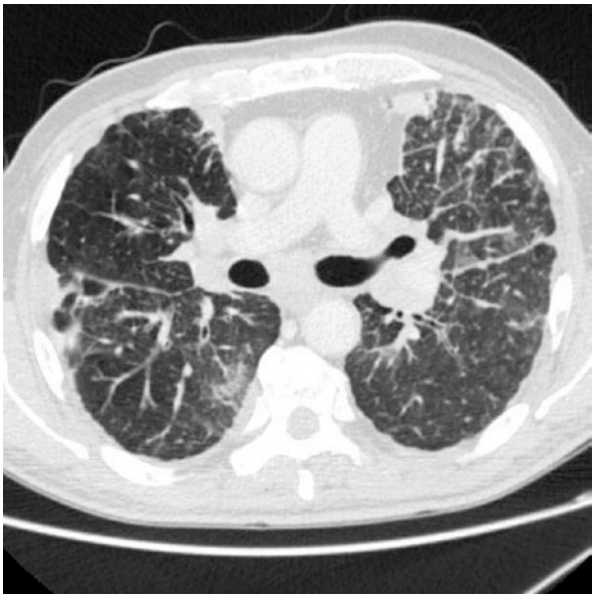

Fig. 5.20 Carcinomatous lymphangiopathy—perilymphatic distribution of nodules

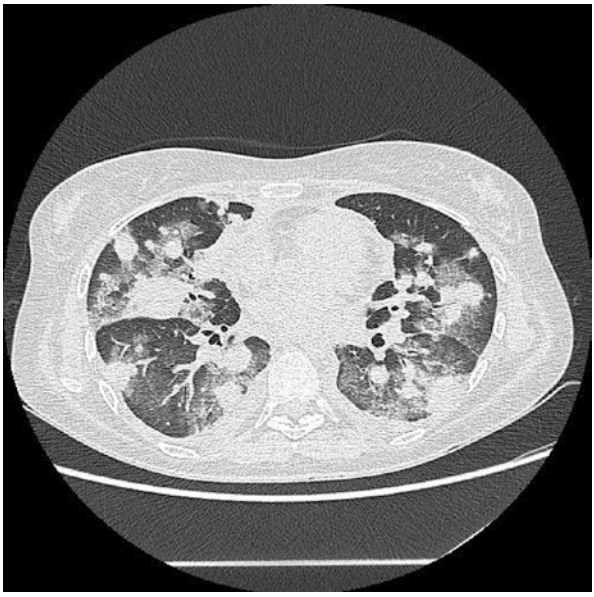

Fig. 5.21 Lymphoma—perilymphatic distribution of nodules

Table 5.2 Perilymphatic distribution

Sarcoidosis
Silicosis
Coalworker's pneumoconiosis
Carcinomatous lymphangiopathy
Amyloidosis
Lymphocytic interstitial pneumonia (LIP)
Lymphoma

5.3.2 Centrilobular Distribution

In the centrilobular distribution (Figs. 5.22, 5.23, 5.24 and 5.25, Table 5.3), the nodules do not reach the pleura (5–10 mm from the fissures or pleura), they are bilateral and evenly distributed. A typical representative is HP.

Tree-in-bud is also a representative of centrilobular pattern (Figs. 5.26 and 5.27). This corresponds to the dilation of the centrilobular bronchiole with pathological content (most commonly occurs in small airway infections—infectious bronchiolitis).

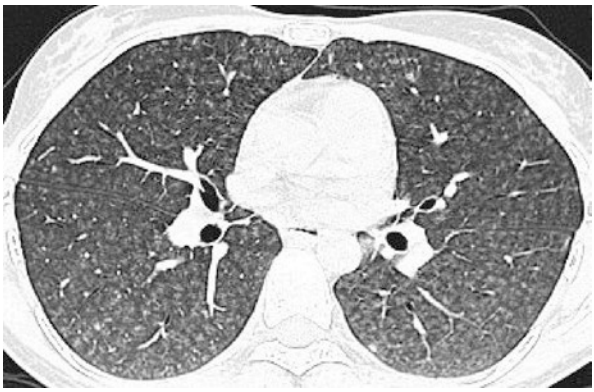

Fig. 5.22 Exogenous allergic alveolitis—centrilobular nodules

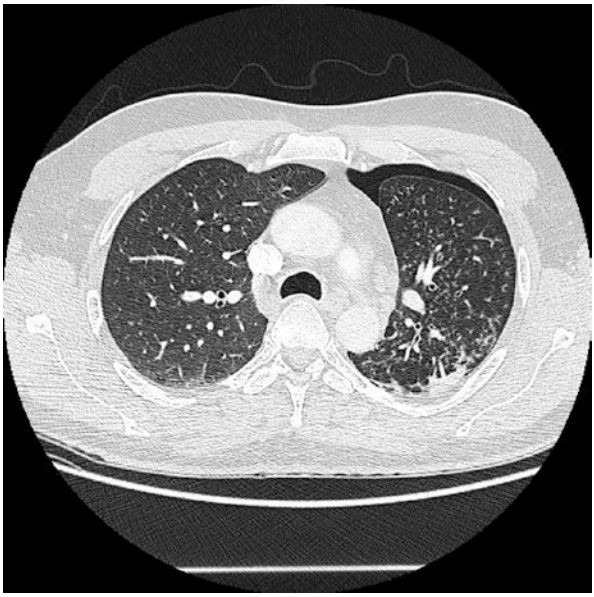

Fig. 5.23 Bronchiolitis (respiratory, infectious, obliterate)—centrilobular nodules

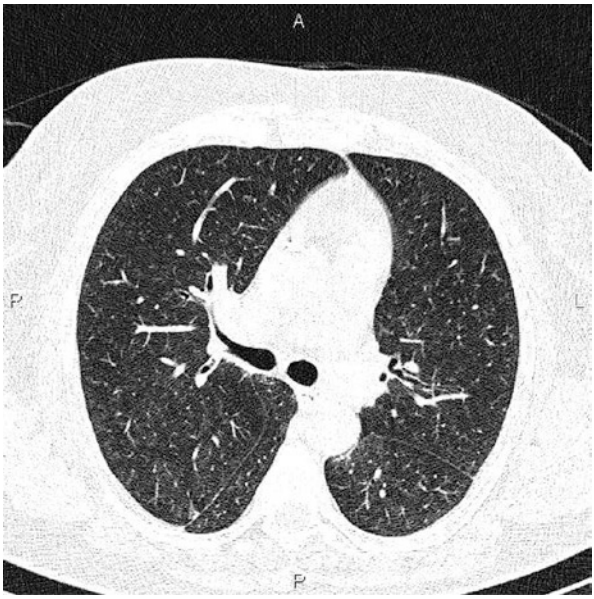

Fig. 5.24 Respiratory bronchiolitis associated with interstitial disability (RB-ILD)—centrilobular nodules

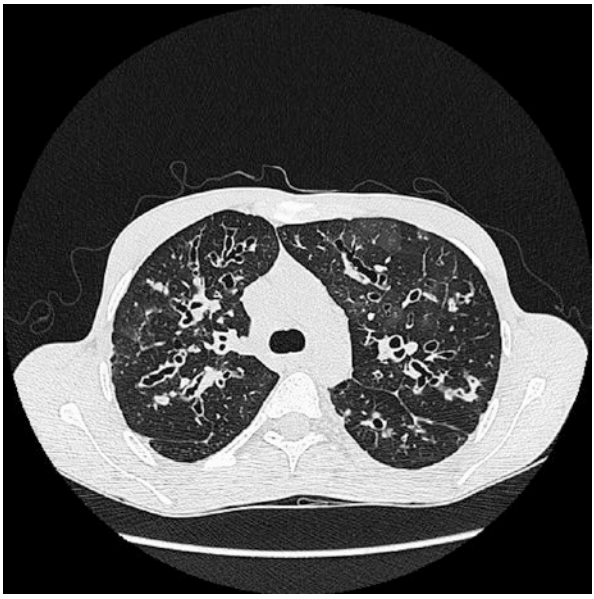

Fig. 5.25 Cystic fibrosis—centrilobular nodules

5.3.3 Random Distribution

The nodules occur randomly in relation to the secondary lobule (Figs. 5.28 and 5.29). The lungs are affected in a diffuse and symmetrical manner. A typical representative is miliary tuberculosis (TB) (Table 5.4).

Table 5.3 Centrilobular distribution

Exogenous allergic alveolitis (EAA)
Bronchiolitis (respiratory, infectious, obliterating)
Respiratory bronchiolitis associated with interstitial disability (RB-ILD)
Cystic fibrosis

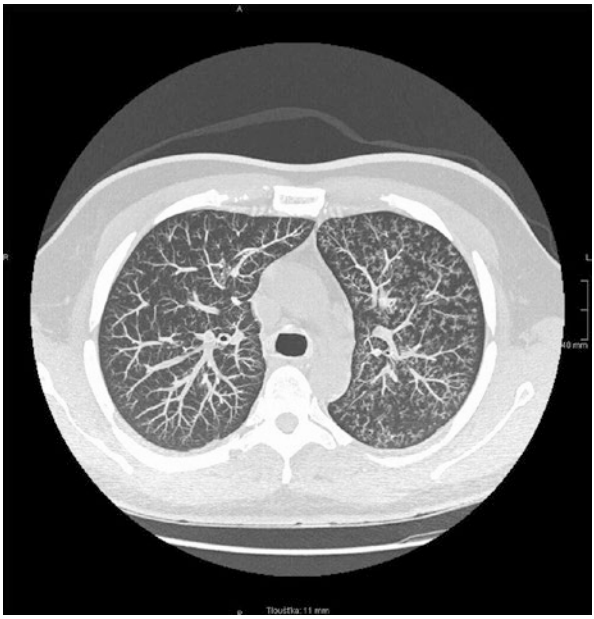

Fig. 5.26 Infectious bronchiolitis—tree-in-bud: centrilobular nodules (tree-in-bud pattern)

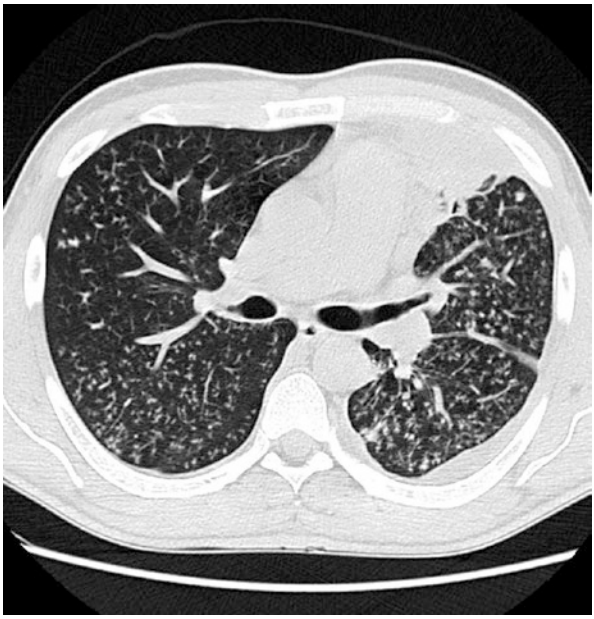

Fig. 5.27 Tuberculosis of lung: centrilobular nodules (tree-in-bud)

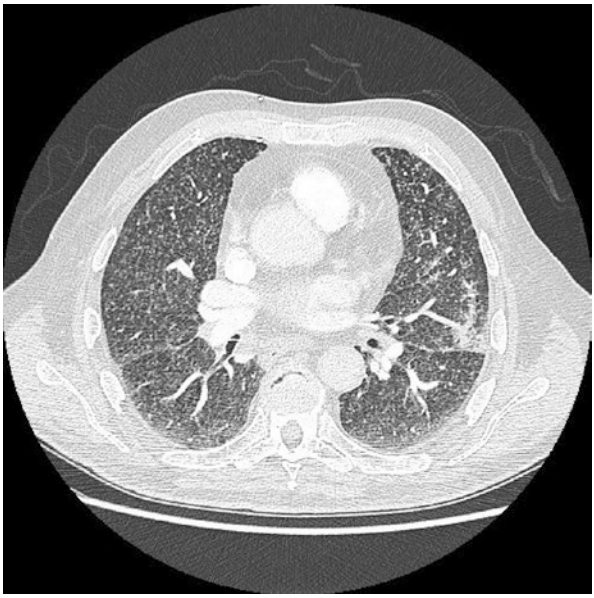

Fig. 5.28 Miliary TB—random distribution of nodules

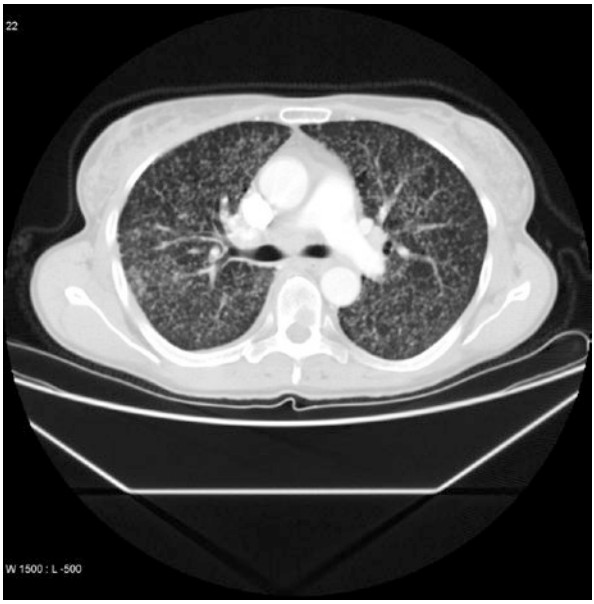

Fig. 5.29 Miliary metastases—random distribution of nodules

Table 5.4 Miliary TB

Miliary TB
Miliary metastases
miliary mycoses

5.4 Increasing Density

Jana Votrubova

The increase in pulmonary tissue density, i.e. decreased lung tissue transparency, arises due to the loss of air or increase in solid tissue or fluid. In the advanced stages of the disease, it is most often a combination of all the above-mentioned causes [1].

Pulmonary tissue consolidation is defined as a local or diffuse increase in the density of the pulmonary parenchyma with invisible vascular structures (note that air-filled bronchi may be visible). The feature of pulmonary tissue consolidation is the replacement of air in the alveoli with fluid, cells, solid matter, or other factors that prevent aeration of the alveoli (Fig. 5.30).

The "ground glass" opacities (GGO) are defined as a local or diffuse increase in the density of the pulmonary parenchyma with visible vascular structures. The basis of the GGO phenomenon is the enhancement of the interalveolar and/or intra-alveolar interstitium, bronchial wall thickening, or the presence of cells or fluid inside the alveoli (Fig. 5.31).

The increase of the density of the pulmonary parenchyma of GGO is very often limited to a certain segment or lobe (Fig. 5.32).

If the GGO affects the centre of the lobule, it creates signs of hazily defined centrilobular nodules (Fig. 5.33) within a normal unreinforced interstitium.

"**Crazy paving**" represents a combination of GGO and linear opacities during the thickening of inter- or intralobular septa and alveolar involvement. It may also be associated with bronchial deformation. Typically presents in radiation pneumonitis and alveolar proteinosis (Figs. 5.34 and 5.35).

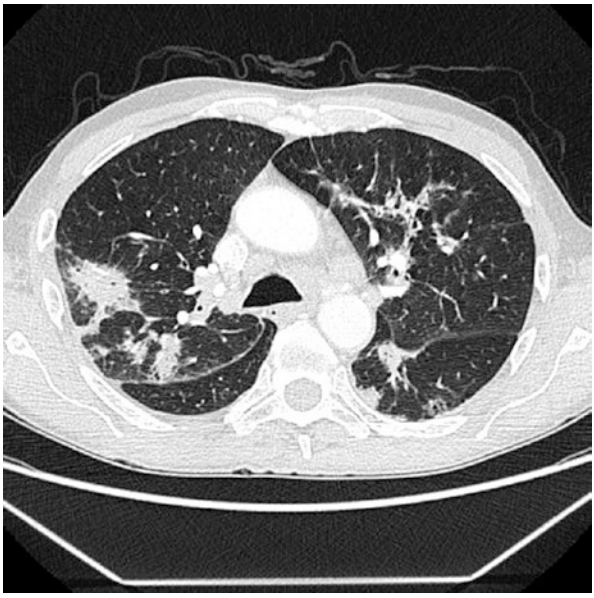

Fig. 5.30 HRCT of the lungs: consolidation of the pulmonary parenchyma (organising pneumonia)

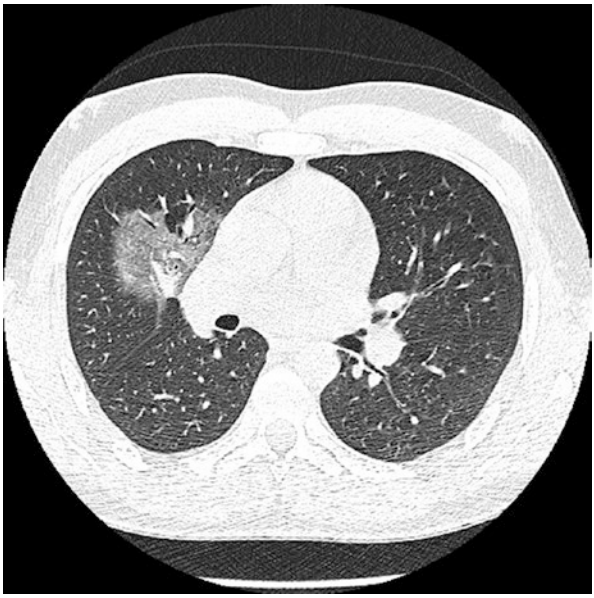

Fig. 5.31 HRCT of the lungs: ground glass opacity (alveolar haemorrhage)

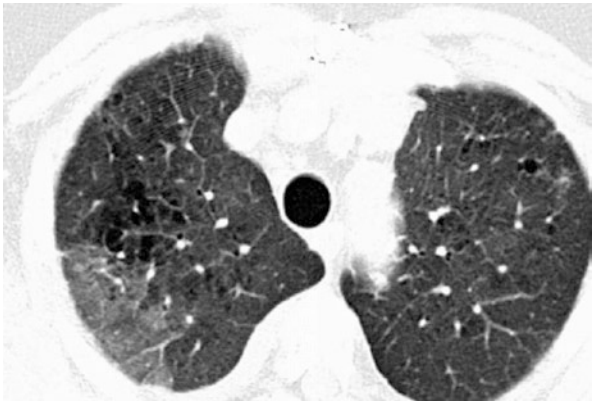

Fig. 5.32 Diffuse increase density of the lung: GGO patterns with accentuation in the right upper lobe dorsolaterally due to pulmonary oedema

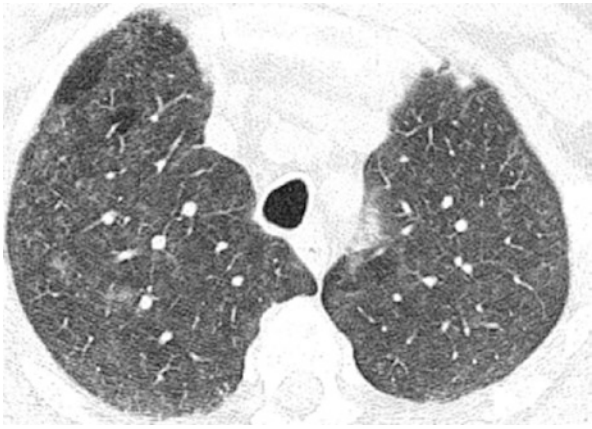

Fig. 5.33 Small centrilobular GGO typical for exogenous allergic alveolitis

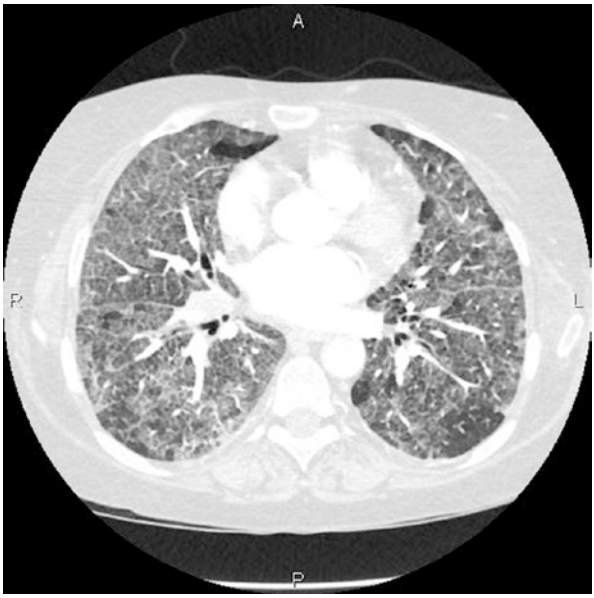

Fig. 5.34 "Crazy paving"—the sign of "irregular pavement"

Fig. 5.35 An illustrative photo of irregular paving—sign of "crazy paving"

"**Mosaic pattern**" represents hypo- and hyperdense regions. It has three variants: (1) the mosaic is formed by mapped regions of GGO, and the hypodense lung is normal, with normal blood vessel translucency; (2) the mosaic image in broncho/bronchial obstruction—hypodense regions with poor vascularisation are abnormal. The differences in density are increased in expiratory scans; (3) mosaic oligemia in cases of chronic thromboembolic pulmonary hypertension—abnormal hypodense areas of hypovascularisation, with no apparent increase of density on the expiratory scans [2].

The mosaic image in combination with normal lung parenchyma, GGO, and pulmonary consolidations is called the "**head cheese**" sign. It is a typical

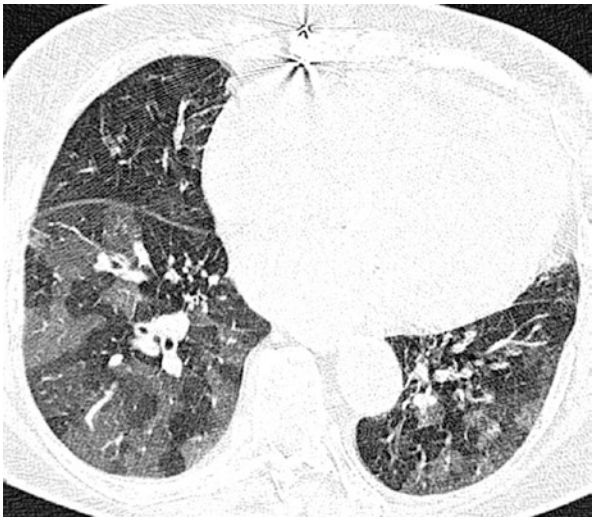

Fig. 5.36 Mosaic attenuation (patient with asthma)

Fig. 5.37 Mosaic attenuation—an illustrative photo of mosaic

phenomenon of HP, typically in its chronic form, asthma, bronchiolitis and pulmonary embolism (Figs. 5.36 and 5.37).

Gas or air-filled bronchi create an impression of "black bronchi" in comparison with the surrounding lung tissue and can be caused by the surrounding increase in density of a GGO pattern ("black bronchus sign") (Fig. 5.38).

The correct interpretation of GGO is essential for the proper diagnosis of an active disease and may indicate impending pulmonary fibrosis.

HRCT is needed to assess the increase in pulmonary parenchyma density, that is CT scans with a hard kernel (Figs. 5.39 and 5.40).

Equally important is the evaluation of expiratory lung CT scans (Fig. 5.41a, b).

The increase in density in the pulmonary parenchyma is confirmed by comparing scans in supinate and pronate position. If GGO is present, there are no changes in density upon altering the patient's position (Fig. 5.42a, b). Lung diseases with typical ground glass opacities are listed in Table 5.5. Typical distribution of ground glass opacities is listed in Table 5.6.

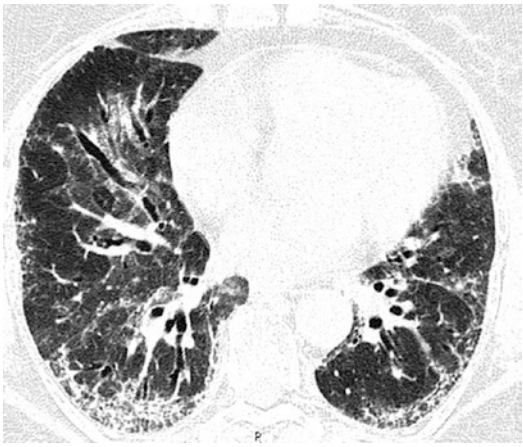

Fig. 5.38 Air bronchogram—air bronchus sign in NSIP

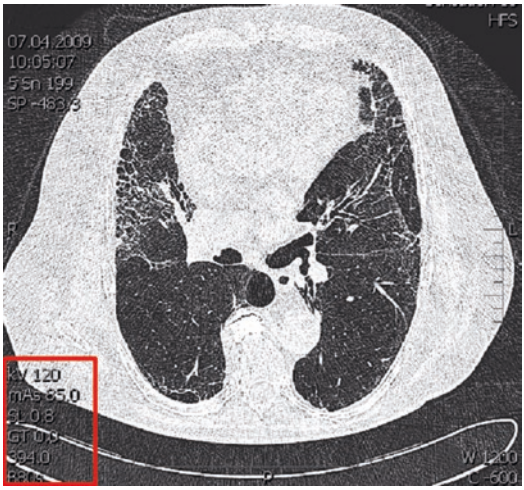

Fig. 5.39 HRCT of the lungs: CT scan in a 1 mm layer/kernel B80—adequate HRCT, where there are clear fibrous changes in both pulmonary lobes—honeycombing without the presence of GGO

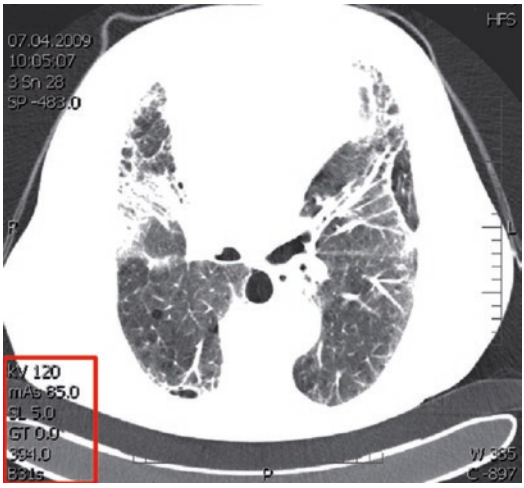

Fig. 5.40 HRCT of the lungs (the same patient, same layer, same date as Fig. 5.39): CT scanned in a 5 mm layer/kernel B31—in a conventional CT it would be incorrect to define a clear decrease of transparency of both pulmonary lobes as the GGO

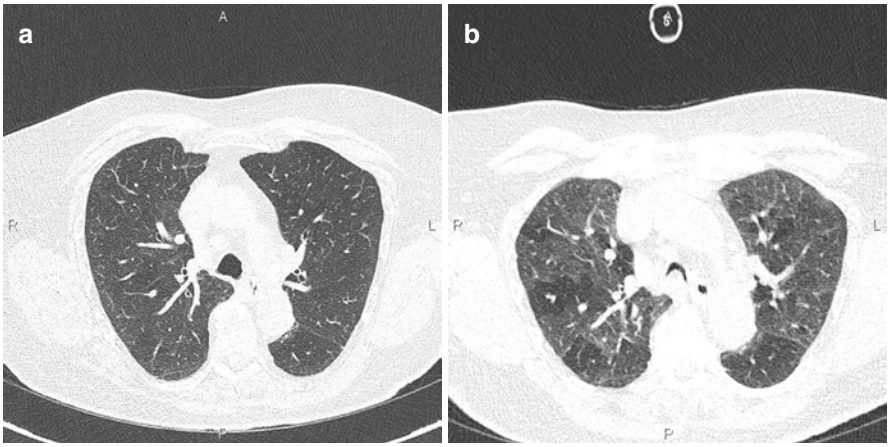

Fig. 5.41 (**a**) HRCT of the lungs during inspiration, the apparent GGO phenomenon dorsally. The rounded shape of the trachea confirms inspiration. (**b**) The same patient, in the same layer done in expiration, where the GGO are highlighted in the dorsal parts, although noted slightly ventrally, where there is in addition the left paramediastinal "air trapping", i.e. pathological retention of air in a certain area of the lungs. The expiration confirms the concavity of the dorsal wall of the trachea

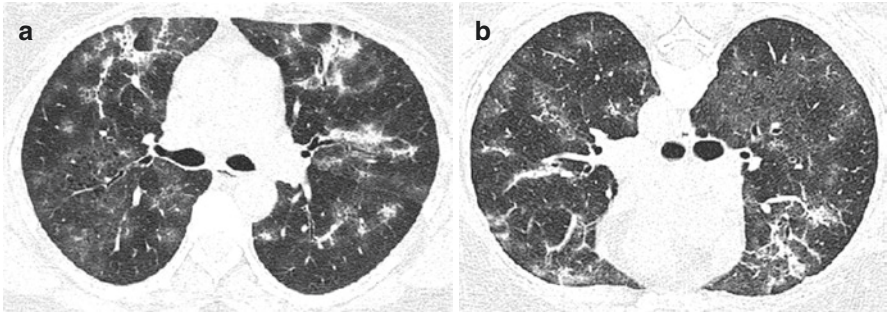

Fig. 5.42 (**a**) HRCT scan of the lungs in supination with an image of fine regions of GGO. In addition, ventrally there are fine fibrous changes. (**b**) The same patient, the same layer, only with the patient rotated on the abdomen. It is clear that the previous image-density changes persist in the pulmonary parenchyma

Table 5.5 Diseases with the typical occurrence of the "ground glass" image

Acute diseases	Chronic diseases
Pulmonary oedema	EAA—chronic stage
DAD/ARDS/AIP	"Smoking related diseases" (RB-ILD, DIP)
Infectious diseases	Interstitial pneumonia (NSIP)
Bleeding	Adenocarcinoma with lepidopteran growth
EAA—acute stage	Organising pneumonia
Eosinophilic pneumonia—acute	Lymphatic interstitial pneumonia
Radiation pneumonitis—acute	Eosinophilic pneumonia—chronic
	Lipoid pneumonia
	Alveolar proteinosis
	Sarcoidosis

DAD diffuse alveolar damage, *ARDS* acute respiratory distress syndrome, *AIP* acute interstitial pneumonia, *EAA* exogenous allergic alveolitis, *RB-ILD* respiratory bronchiolitis interstitial lung disease, *DIP* desquamative interstitial pneumonia, *NSIP* non-specific interstitial pneumonia

Table 5.6 Typical distribution of "ground glass" image

Diffuse	Localised
Pulmonary oedema	Infection
DAD/ARDS/AIP	Sarcoidosis
Infection (viral)	Organising pneumonia
Bleeding	Adenocarcinoma with lepidopteran growth
Adenocarcinoma with lepidopteran growth	Bleeding
Alveolar proteinosis	Eosinophilic pneumonia
Interstitial pneumonia	EAA

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Part II

Cases According to Dominant Patterns

Low Attenuation Patterns

6

Martina Sterclova, Jana Votrubova, Eva Kocova, Vladimir Bartos, Filip Ctvrtlik, Monika Zurkova, and Vladimíra Lostakova

6.1 Pulmonary Langerhans Cell Histiocytosis I

Martina Sterclova, Jana Votrubova, and Eva Kocova

Female, 22 years old.
Patient presents with a cough.

Medical History

- Until now, the patient has been healthy.
- Family history: her grandmother died of idiopathic pulmonary fibrosis—rapid progression (death after 6 months from diagnosis).

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_6

Occupational History and Exposure

- Hotel receptionist.
- Lives with family, in the family house, and has a dog which remains outdoors.
- Smoking history: smoked 10–20 cigarettes a day from the age of 12 to 16 years old.

History of Present Complaint

- Caught a cold half a year ago, and since then a dry cough persists with no response to treatment, including repeated antibiotic therapy.

Objective Finding

- Normal findings with vesicular breathing, patent airways, and without secondary phenomena.

Examination

Lung Functional Tests

- VC_{max} 3.83 L/92% (ref. v), FVC 3.51 L/79% (ref. v), FEV_1 2.78 L/72% (ref. v), TLC 5.63 L/99% (ref. v), RV 1.80 L/116% (ref. v), DL_{CO} 7.11/69% (ref. v), K_{CO} 1.67/93% (ref. v).
- Mild obstructive ventilatory defect, with a slightly decreased forced vital capacity. There is a normal resting maximum vital capacity, without pulmonary hyperinflation, but with a slightly reduced diffusion capacity for carbon monoxide.
- 6-min walk test—490 m, i.e. normal performance, without the presence of latent respiratory insufficiency (O_2 saturation by pulse oximetry 97…97…95…97%).

Radiology

- *Posteroanterior chest X-ray*: Diffuse reticulations, especially in the upper and middle lung fields (Fig. 6.1).
- *HRCT of the lungs*: Multiple thin-walled cysts in both lungs, especially in the upper lobes, with fewer cysts caudally. Posterior costophrenic angles are without cysts. Rare small centrilobular nodules were identified (Fig. 6.2a–c).

6.1.1 Multidisciplinary Team and Differential Diagnosis

Female with cystic lung disease with small centrilobular nodules in a young smoker. According to HRCT, it implies a typical image of pulmonary histiocytosis.

MDT Conclusion: Clinically and radiologically this is suggestive of pulmonary histiocytosis. It is recommended to perform a BAL, and to exclude systemic connective tissue disease (SCTD) or immunodeficiency. In the case of unclear results, a histological verification of the lung process must be performed.

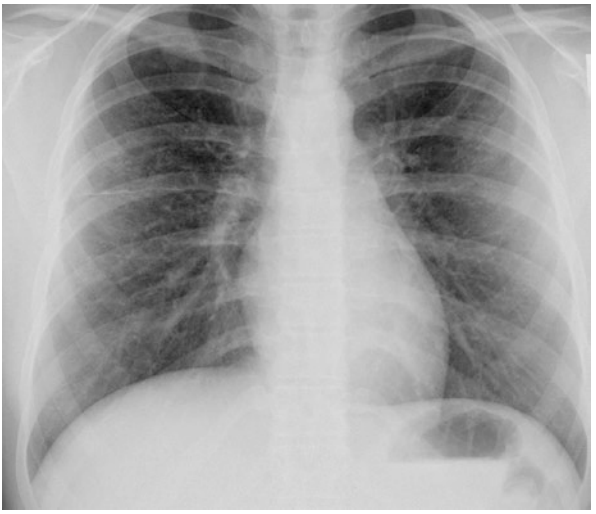


Fig. 6.1 Posteroanterior chest X-ray: reticulations in the upper and middle lung fields

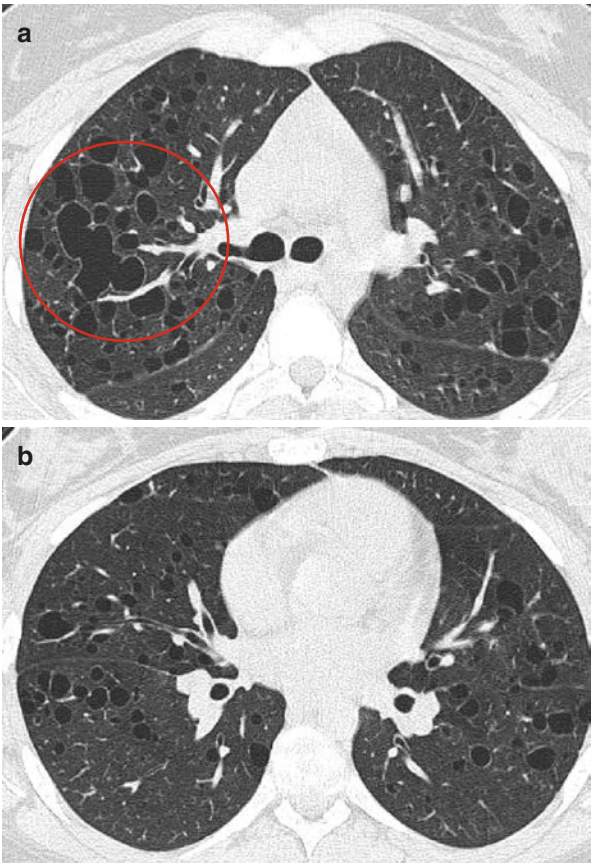
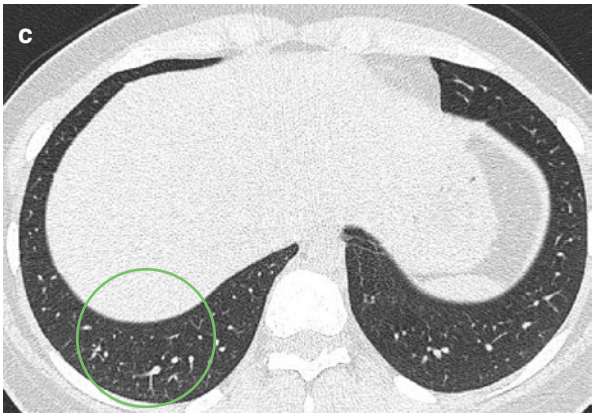


Fig. 6.2 (**a**) HRCT of the lungs: multiple bizarre thin-walled cysts, especially in the upper lobes. Rare, small centrilobular nodules. (**b**) HRCT of the lungs: multiple bizarre thin-walled cysts, especially in the upper lobes. (**c**) HRCT of the lungs: Basal parts (posterior costophrenic angles) of the lungs without cysts

Fig. 6.2 (continued)



Bronchoalveolar Lavage (BAL)

- Cellular rich material composed of a differential count of 83% macrophages, 6% lymphocytes, 1% neutrophils, and 10% eosinophils. An immunohistochemical analysis revealed an increase in the presence of Langerhans cells (CD1a+, S100 protein positive), above 5%.

Rheumatological Screening and Immunocompetence Tests

- No evidence of autoantibodies, SCTD, or cellular or antibody immunodeficiency has been identified.

6.1.2 Conclusion

The findings are compatible with the diagnosis of pulmonary Langerhans cell histiocytosis (PLCH). The patient refused any form of histological verification for the fear of complications that may occur, and due to her symptoms reducing after quitting smoking.

During follow-up investigations, the cough improved, the patient was without any difficulties and began to participate in sports. A year later, HRCT of the lungs findings were stationary. Pulmonary function improved, the obstruction retreated, and there was only a slight limitation of pulmonary diffusion capacity. Corticotherapy was not necessary for this patient.

6.1.3 Pulmonary Histiocytosis

Pulmonary histiocytosis is a smoking-related lung disease. On HRCT, there are apparent centrilobular nodules of up to 10 mm in size, which can cavitate. In later

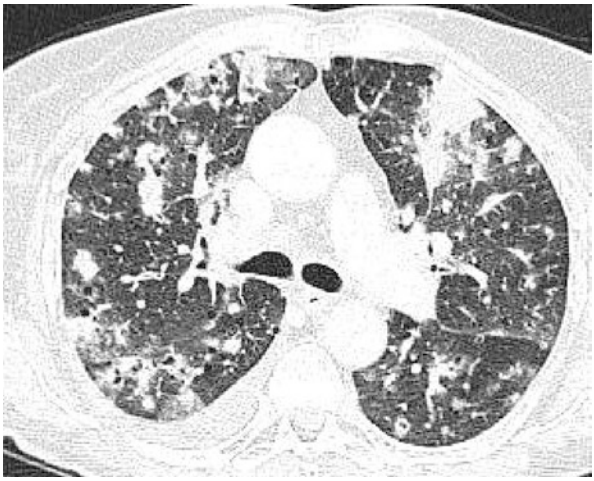


Fig. 6.3 HRCT of the lungs: Bronchogenic lung carcinoma in a patient with pulmonary histiocytosis

stages of the disease, cyst formation can prevail, which are thin-walled and typically of bizarre shapes (this is by combination of two or more cysts). In the differential diagnosis, it is essential that the posterior costophrenic angles are not affected. The presence of centrilobular nodules is typical of pulmonary histiocytosis.

Note

- For cystic pulmonary diseases, it is necessary to evaluate the presence and absence of the cyst wall, cyst distribution, their shape and the eventual coincidence of cysts and nodules.
- Clinically, a history of smoking is significant.
- In the BAL of PLCH, the presence of Langerhans (CD1a positive) cells is increased to at least above 5% (if not, then the finding does not exclude PLCH, but however histological verification is required for the diagnosis). In the early stages, nodules and cysts with thin and even thick walls are clearly visible.
- Frequent complications are pneumothorax, and eventually the development of bronchogenic lung carcinoma (Fig. 6.3).

6.1.4 Pulmonary Langerhans Cell Histiocytosis—What We Should Consider in the Differential Diagnosis

1. Lymphangioleiomyomatosis: Regular cysts affecting the entire lungs (including the posterior costophrenic angles) (Fig. 6.4).
2. Lymphocytic interstitial pneumonia: Typically, in autoimmune diseases, thin-walled cysts especially in the lower lobes, perivascularly, and without nodular involvement (Fig. 6.5).

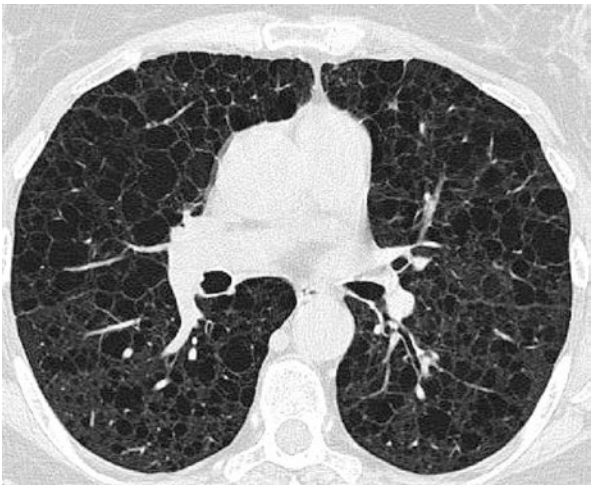


Fig. 6.4 Lymphangioleiomyomatosis: regular cysts affecting the entire lungs

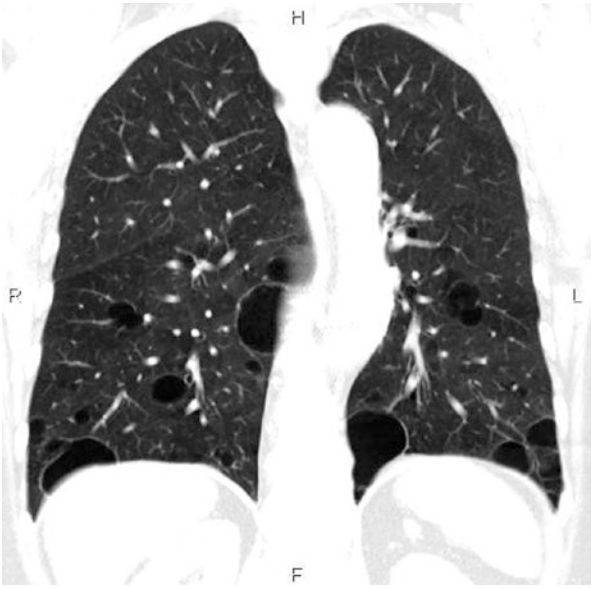


Fig. 6.5 Lymphocytic interstitial pneumonia: thin-walled cysts especially in the lower lobes

3. Centrilobular pulmonary emphysema: "Holes" without walls, centrilobular, without nodules (Fig. 6.6).
4. Cystic bronchiectasis—e.g. allergic bronchopulmonary aspergillosis (ABPA): illustrate continuity with the bronchial tree, alveolar opacities, and bronchial mucosal involvement (Fig. 6.7).

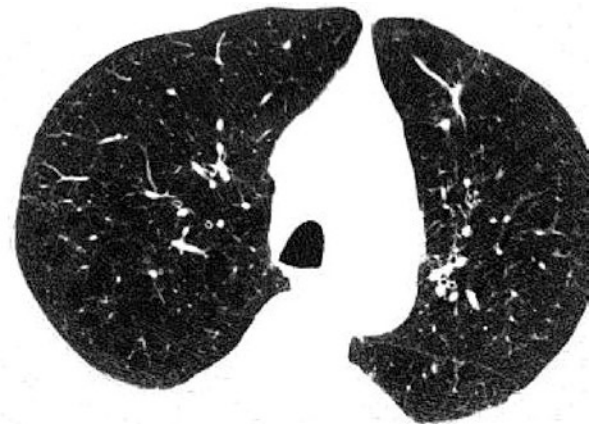


Fig. 6.6 Centrilobular pulmonary emphysema

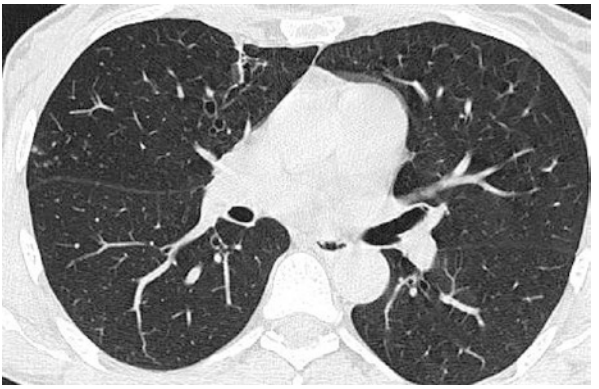


Fig. 6.7 Cystic bronchiectasis in the right upper lobe

6.2 Pulmonary Langerhans Cell Histiocytosis II

Martina Sterclova and Jana Votrubova

Female, 32 years old.
Patient presents with a 1-week history of dyspnoea and cough, and an initial fever.

Medical History

- Until the presentation, the patient was completely healthy

Occupational History and Exposure

- Unemployed, never worked, a housewife
- No pets, no pigeons in the proximity of the house, and does not visit whirlpools or swimming pools
- Smoking history: since the age of 15, 1 cigarette a day

History of Present Complaint

- One week ago, the patient had a temperature reaching 39 °C, and complained of a cough and exertional dyspnoea. Fever receded after 3 days of self-treatment with paracetamol. Cough prevails, and the patient produces clear sputum. Additionally, she experiences shortness of breath whilst walking on a flat surface.

Objective Finding

- Bilateral vesicular breathing, without secondary phenomena.

Examination

Lung Functional Tests

- FVC 2.79 L/91% (ref. v), FEV_1 2.29 L/87% (ref. v), FEV_1/FVC 82%, VC_{max} 2.91 L/95% (ref. v), TLC 4.22 L/98% (ref. v), DL_{CO} 4.24/52% (ref. v)
- Pulmonary function tests indicate no signs of restrictive or obstructive ventilatory disorder. The transfer factor is moderate to severely decreased.

Radiology

- *Posteroanterior and lateral chest X-ray*: Fine reticulonodulations mainly in the upper lung fields (Fig. 6.8a, b).
- *HRCT of the lungs*: Combination of small nodules and cysts with a predilection to the upper lobes and the middle lobes of the right lung with minor changes in the lower lobes. It is a highly specific image for the diagnosis of PLCH (Fig. 6.9a–c).

Sputum

- *Mycobacterium tuberculosis* identified microscopically, BACTEC negative.

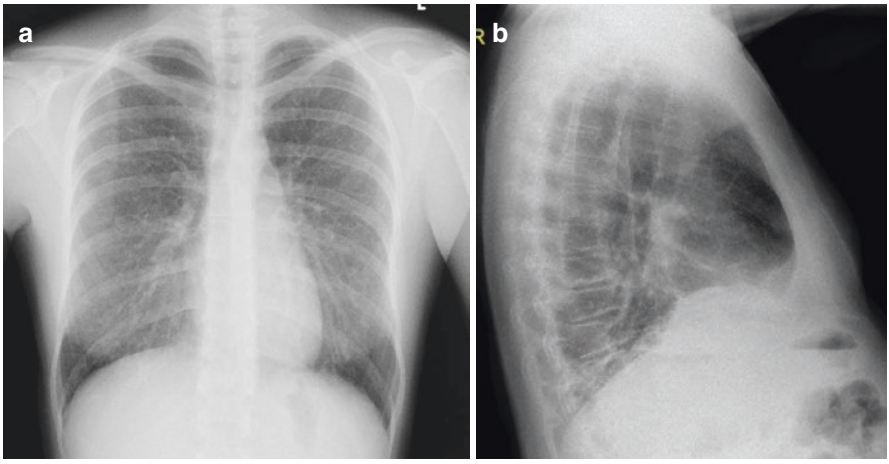


Fig. 6.8 (**a**) Posteroanterior chest X-ray: fine reticulonodulations mainly in the upper lung fields. (**b**) Lateral chest X-ray: fine reticulonodulations

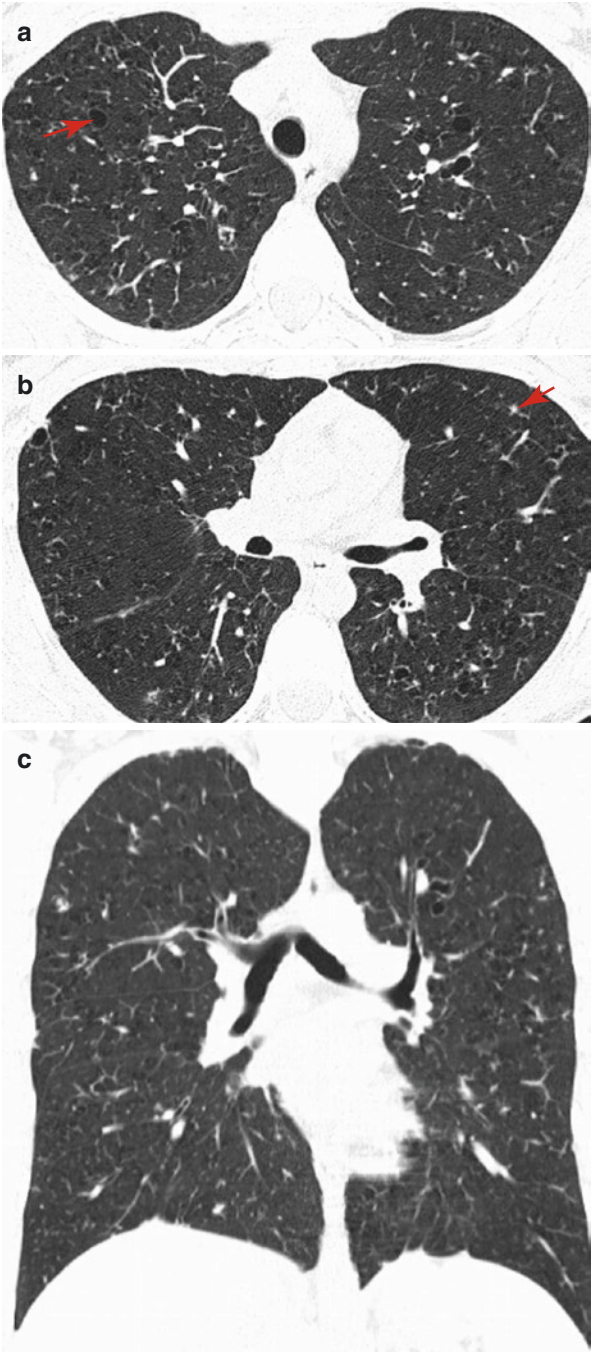


Fig. 6.9 (**a**) HRCT of the lungs: a combination of small nodules and cysts in the upper lobes—a highly specific sign for the diagnosis of PLCH. (**b**) HRCT of the lungs: a combination of small nodules and cysts with a predilection in the upper lobes and the middle lobe of the right lung—a highly specific sign for the diagnosis of PLCH. (**c**) HRCT of the lungs: coronal reconstruction a combination of small nodules and cysts with a predilection in the upper lobes and the middle lobe of the right lung with minor changes in the lower lobes—a highly specific image for the diagnosis of PLCH

Bronchoscopy with Bronchoalveolar Lavage
- BAL findings: Alveolar macrophages 96%, lymphocytes 3% and neutrophils 1%.
- Microscopically, PCR and BACTEC do not confirm *M. tuberculosis*.

6.2.1 Multidisciplinary Team and Differential Diagnosis

The patient is a smoker, and in light of the diffuse pathology findings, tuberculosis is unlikely. The CT findings of many small cavities are suspected to PLCH ad requires biopsy verification. An atypical resection of the upper and lower pulmonary lobes via video-assisted thoracoscopy (VATS) is indicated.

Histology
The pathological findings of the pulmonary parenchyma are related to chronic nicotinism, chronic bronchitis, bronchiolitis, and PLCH.

6.2.2 Conclusion

Diagnosis of PLCH, with a corresponding radiological sign, supported further by histological analysis.

The patient has been advised to quit smoking, including passive exposure to tobacco smoke.

6.2.3 Pulmonary Langerhans Cell Histiocytosis (PLCH)

PLCH usually affects young patients with a history of nicotinism. It can also be a random finding, as it is asymptomatic in up to a quarter of the patients. Usually, the disease manifests with a cough, exertional dyspnoea, and sometimes by a fever, weight loss or night sweats. The first symptom may be spontaneous pneumothorax. Typical HRCT in the early stages of the disease includes multiple centrilobular, but also peribronchial irregular nodules. Late stages of the disease present multiple cysts with walls of different thickness, sometimes merging together. Primarily the upper lobes are affected. Nodules and cysts often occur concurrently. The definitive diagnosis of PLCH requires the histological analysis of Langerhans cell granulomas.

Note

- In the adult population, PLCH affects exclusively young smokers, and although the definitive diagnosis is based on a histological image, the HRCT findings are typical, with multiple nodules and/or cysts affecting predominantly the upper and middle pulmonary lobes.
- The primary therapeutic measure is to avoid further exposure to tobacco smoke.
- If untreated, it can progress to the development of severe pulmonary hypertension, predominantly affecting the venules.

6.2.4 Pulmonary Langerhans Cell Histiocytosis—What We Should Consider in the Differential Diagnosis

6.2.4.1 Differential Diagnosis of Nodular Pulmonary Pathology

1. Pulmonary sarcoidosis: Nodules in a perilymphatic distribution, symmetrical lymphadenopathy, and calcified nodes (Fig. 6.10).
2. Metastatic lung disorder: History of oncological disease, with a random distribution of nodules (Fig. 6.11).

The following would also come into consideration: Pulmonary tuberculosis, Pneumonia caused by an atypical agent.

6.2.4.2 Differential Diagnosis of Pulmonary Diseases with Cysts on HRCT of Lung

3. Lymphangioleiomyomatosis: Thin-walled cysts surrounded by an intact pulmonary parenchyma is typical. In the more progressed stages, the number of cysts increases and normal pulmonary parenchyma decreases (Fig. 6.12).
4. Lymphocytic interstitial pneumonia: Occurs almost in Sjögren's syndrome. A diffuse pathology of the interstitium, with the combination of dominating GGO and thin-walled cysts in a perivascular distribution (Fig. 6.13).

Following would also come into consideration: pulmonary amyloidosis, light chain deposition disease, pneumocystis pneumonia, metastatic lung disease during generalised sarcomas or rare Birt-Hogg-Dube syndrome.

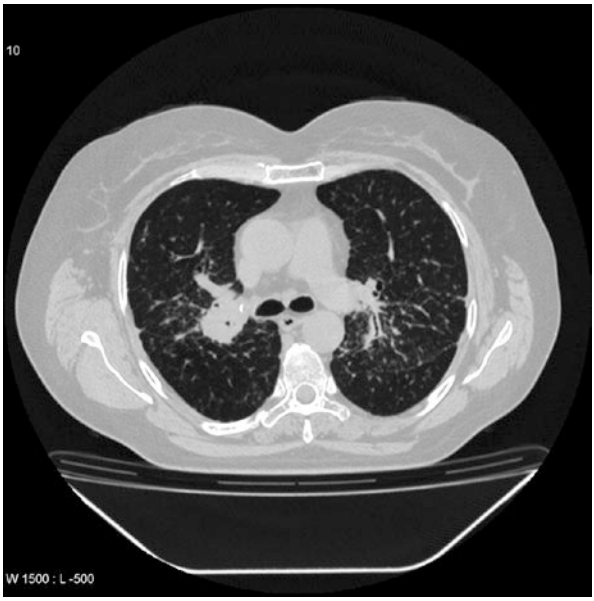


Fig. 6.10 Pulmonary sarcoidosis: Nodules in a perilymphatic distribution, lymphadenopathy with calcification

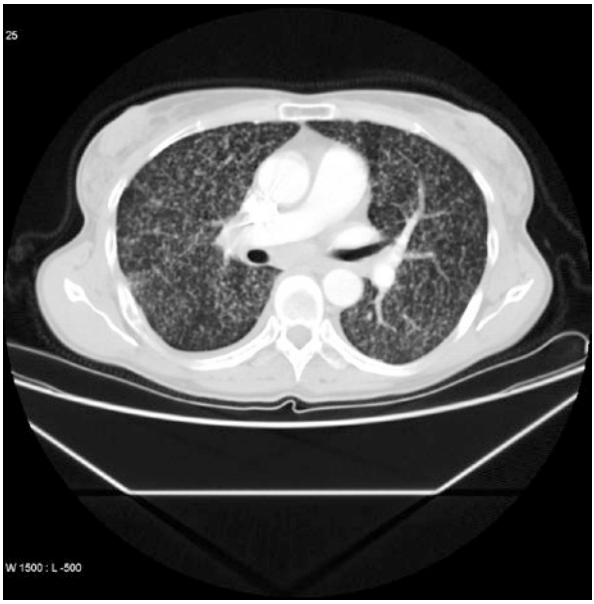


Fig. 6.11 Metastases in the lung: random distribution of nodules

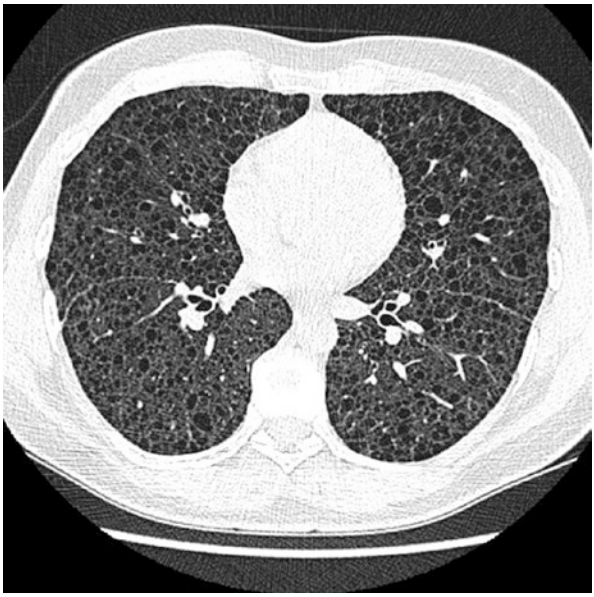


Fig. 6.12 Lymphangioleiomyomatosis: Thin-walled cysts surrounded by an intact pulmonary parenchyma is typical

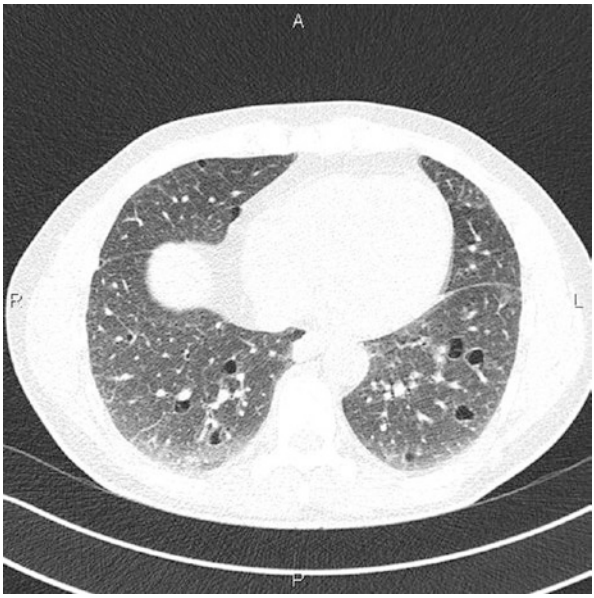


Fig. 6.13 Lymphocytic interstitial pneumonia: GGO with thin-walled cysts in a perivascular distribution

6.3 Lymphangioleiomyomatosis I

Eva Kocova and Vladimir Bartos

Female, 64 years old.
The patient presented with increasing exertional dyspnoea, without a cough.

Medical History

- Recurrent bilateral pneumothoraces—10 in total, treated with repeated chest drainage (the first episode occurred at 33 years of age, never operated on). Is in treatment for eosinophilic asthma with progressive bronchial obstruction. Otherwise, the patient has no other issues and remains healthy

Occupational History and Exposure

- A pensioner, previously employed as a clerk, with no history of hazardous work
- Lives in a family home without pets
- Social history: lifelong non-smoker
- Medication history: long-term inhaled corticosteroids and long-term bronchodilator inhalation therapy, otherwise without further medications

History of Present Complaint

- The patient has observed dyspnoea since childhood, repeated pneumothoraces since the 33 years of age, and currently is treated for asthma. Last month, despite asthma treatment the patient notes increasing exertional dyspnoea and is referred for re-evaluation.

Objective Findings

- Face afflicted by exanthema of adenoma sebaceum, predominantly around the nose.
- Vesicular breathing with a few bilateral coarse rales, without crepitations, and without clubbing of the nails. Other physical findings remain unremarkable.

Examination

Lung Functional Tests

- VC_{max} 2.71 L/109% (ref. v), FEV_1 1.45 L/69% (ref. v), Tiff. 54% (ref. v), MEF50 0.85 L/24% (ref. v), TLC 5.09 L/108% (ref. v), RV 2.39 L/127% (ref. v), RV/TLC 47, DL_{CO} 2.47/34% (ref. v), K_{CO} 0.60/39% (ref. v)
- Indicative of a mild to moderate obstructive ventilatory disorder with hyperinflation, and a severely impaired CO diffusion capacity
- Bronchodilator test with salbutamol was negative
- NO in exhaled air 70 PPB, i.e. signs of eosinophilic airways inflammation
- 6-min walk test—the patient walked 420 m (normal), oxygen saturation at rest was 96%, however, on exertion she desaturated to 85%, i.e. latent respiratory insufficiency

Radiology

- *Posteroanterior chest X-ray*: Bilateral reticulation (Fig. 6.14).
- *HRCT of the lungs*: Bilateral diffuse multiple thin-walled cysts, also present in the posterior costophrenic angles. No nodules and no significant lymphadenopathy. Peripherally, cranial segments of the kidneys with multiple fat densities (Fig. 6.15a–d).

Bronchoscopy and Bronchoalveolar Lavage

- Bronchoscopy reveals anatomically normal findings bilaterally.
- BAL: 79% alveolar macrophages, 18% lymphocytes, an immunoregulatory index of 1.4, 2% of neutrophils and 1% of eosinophils, without any evidence of malignant cells or infection.
- The immunocytochemical detection of antigens CD1a and S100 are negative.

Auxiliary and Laboratory Examinations

- Blood count and biochemical investigations of serum are completely unremarkable.
- The rheumatologic screening is normal with no autoantibodies found.

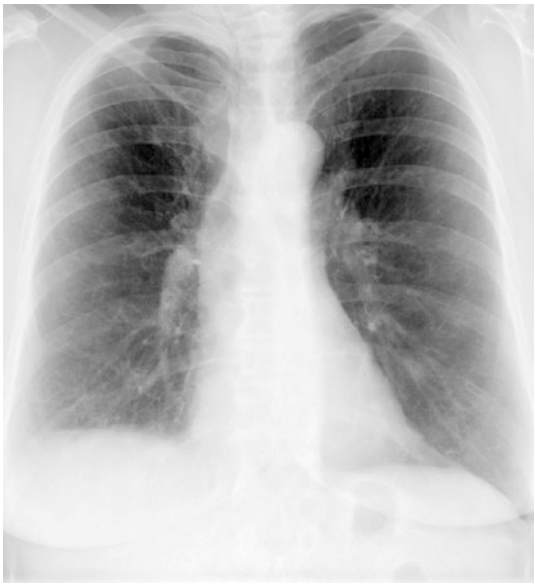


Fig. 6.14 Posteroanterior chest X-ray: bilateral fine reticulations

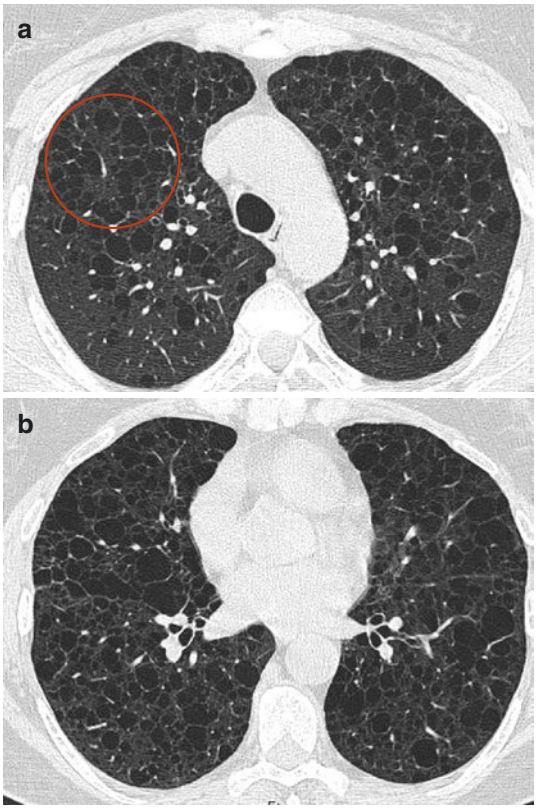
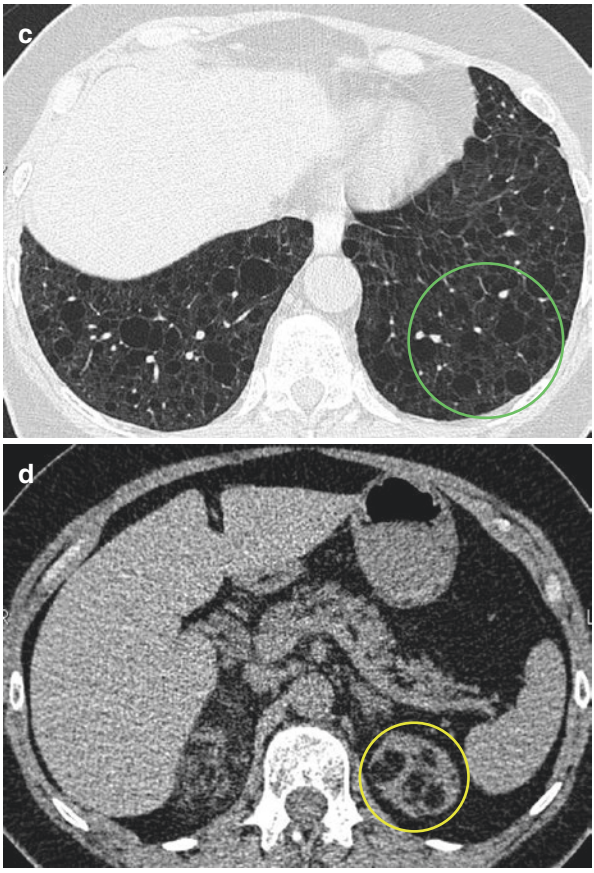


Fig. 6.15 (**a**, **b**) HRCT of the lungs: multiple thin-walled cysts. (**c**) HRCT of the lungs: thin-walled cysts, including posterior costophrenic angles. (**d**) HRCT of upper abdomen (mediastinal window): kidneys with multiple fat densities

Fig. 6.15 (continued)



- Total IgE and immunoglobulin levels are normal, and there is no proof of immunodeficiency or HIV, normal α_1-antitrypsin values. The echocardiogram is satisfactory, except for the finding of mild pulmonary hypertension.

6.3.1 Multidisciplinary Team and Differential Diagnosis

According to HRCT of lungs, there are multiple cysts within the entire lung parenchyma, including the posterior costophrenic angles, without nodular formation. Renal angiomyolipomas were captured peripherally; thus, the HRCT image is typical for lymphangioleiomyomatosis. According to the BAL, pulmonary histiocytosis was not confirmed (and the patient is a lifelong non-smoker). Typical findings of skin adenoma sebaceum are present (confirmed histologically and by a dermatologist).

The conclusion of the MDT: Clinically and radiologically, the most likely cause is pulmonary lymphangioleiomyomatosis, with skin and kidney affliction. There is a suspicion of tuberous sclerosis, and suitable follow-up with magnetic resonance imaging of the brain and a genetic testing is recommended.

6.3.2 Conclusion

Magnetic resonance imaging confirmed the presence of a typical subependymal T2 hyperintense deposition characteristic of tuberous sclerosis, confirming the final diagnosis. The patient would agree to histological verification from the lungs only in case of recurrence of a pneumothorax. So far, this has not yet occurred. Certain regime measures were recommended. Corticotherapy has not been initiated as yet. In course of the years, there was only a very gradual decline in the pulmonary function. An ultrasound scan of the abdomen discovered progressive angiomyolipomas of both kidneys. Genetic testing for mutations for tuberous sclerosis was negative.

Note

- Tuberous sclerosis is a multi-organ disease most commonly affecting the nervous system, skin, lungs, and the kidneys. It is associated with an increased incidence of tumours from the embryonic ectoderm.
- The nature of pulmonary affliction in tuberous sclerosis is of cystic lung disease, typically affecting the whole of the lungs, including the dorsal costophrenic angles. A common complication is the recurrence of pneumothoraces and chylothoraces (Fig. 6.16).

6.3.3 Lymphangioleiomyomatosis—Tuberous Sclerosis—What We Should Consider in the Differential Diagnosis

1. Lymphangioleiomyomatosis (without diagnosis tuberous sclerosis): The radiological signs of the pathological lung are indistinguishable (Fig. 6.17).

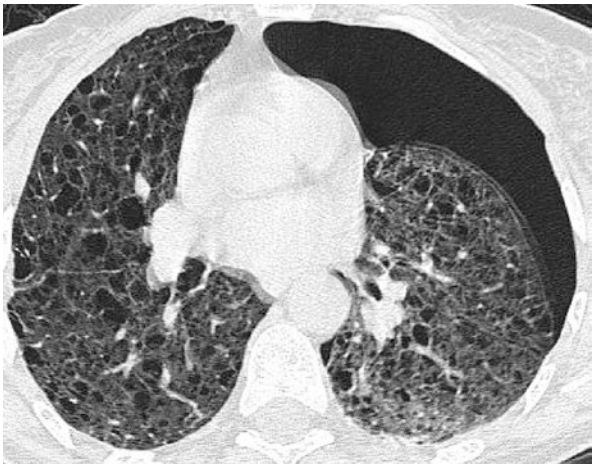


Fig. 6.16 Multiple cysts in patient with lymphangioleiomyomatosis and ventral pneumothorax on the left

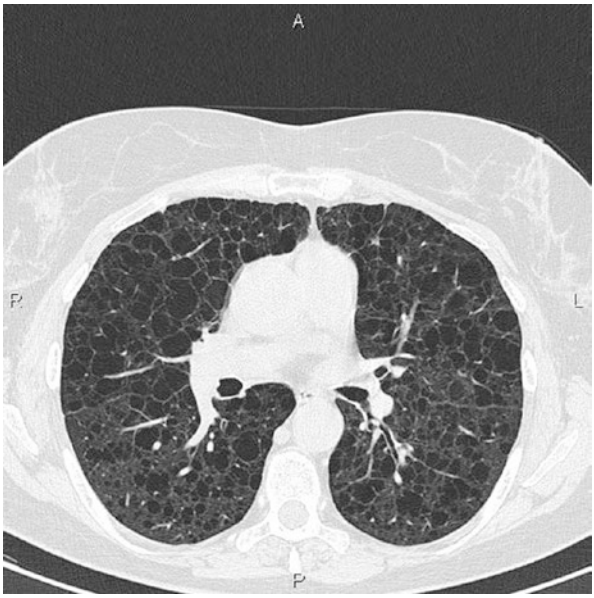


Fig. 6.17 Lymphangioleiomyomatosis—multiple thin-walled cysts

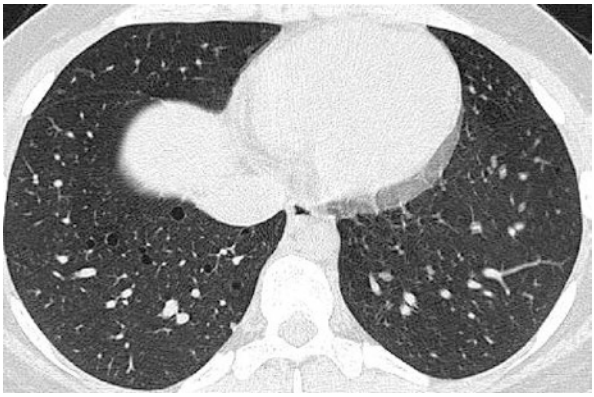


Fig. 6.18 Pulmonary histiocytosis: cystic lesions with a maximum predilection in the upper and middle pulmonary fields, not present in the posterior costophrenic angles

2. Pulmonary histiocytosis: A history of smoking, and cystic lesions with a maximum predilection in the upper and middle pulmonary fields, not present in the posterior costophrenic angles. Multiple nodules are present in early stage (Fig. 6.18).
3. Lymphocytic interstitial pneumonia: Smoothly bordered cysts, especially in the perilymphatic and subpleural region, often associated with autoimmune disease (Fig. 6.19).

The following would also come into consideration: other cystic diseases—see case report 6 Pulmonary Langerhans cell histiocytosis I.

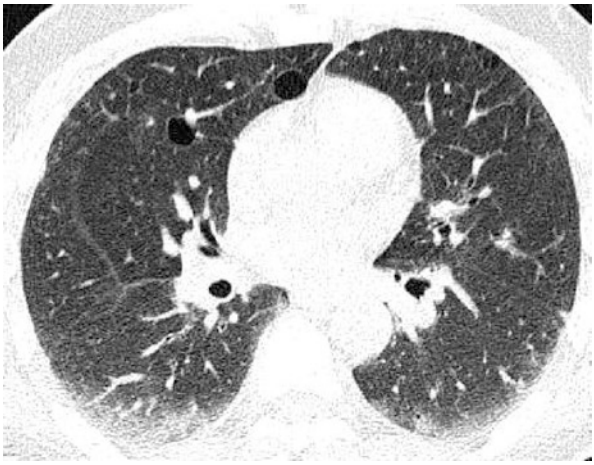


Fig. 6.19 Lymphocytic interstitial pneumonia: Smoothly bordered cysts, especially in the perivascular distribution with GGO

6.4 Lymphangioleiomyomatosis II

Filip Ctvrtlik, Monika Zurkova, and Vladimira Lostakova

Female, 42 years old.
An incidental finding of angiomyolipoma, on an abdominal CT (performed for abdominal pain).

Medical History

- Epilepsy in childhood
- Hysterectomy for uterine fibroids, metrorrhagia, gestational diabetes mellitus, and arterial hypertension

Occupational History and Exposure

- Livestock (cattle) attendant, non-smoker

History of Present Compliant

- The patient was examined for abdominal pain. Ultrasound showed unclear findings of multiple expansions on both kidneys. The CT scan of the kidneys illustrated multiple solid formations bilaterally, with prevailing fat densities characteristic of kidney angiomyolipoma (Fig. 6.20).
- Peripherally were seen multiple small uniform cysts within the lung parenchyma. Follow-up lung CT showed multiple small uniform cysts in the lung parenchyma. Additionally, multiple small sclerotic depositions were also apparent, particularly in the vertebral bodies (Fig. 6.21). The patient was referred to a specialist pulmonary department.

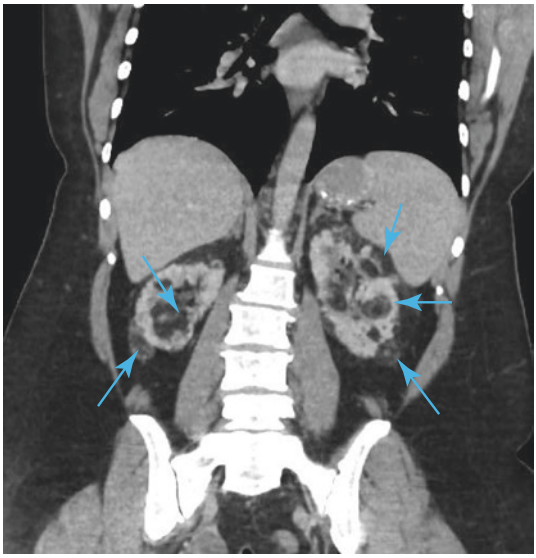


Fig. 6.20 CT scan of the kidneys: multiple renal angiomyolipomas

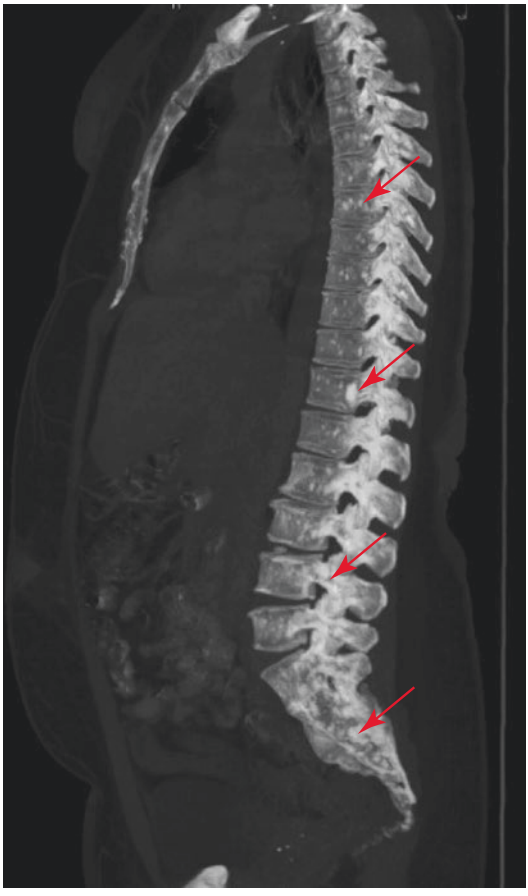


Fig. 6.21 CT scan of the lungs and abdomen (sagittal reconstruction, bone window): multiple small skeletal sclerotic lesions

Objective Finding

- Vesicular breathing, without secondary phenomena.

Examination

Lung Functional Tests
- VC 4.30 L/103% (ref. v), FEV_1 2.93 L/81% (ref. v), FEV_1/VC 68% (ref. v), FEF75 38% (ref. v), TLC 102% (ref. v).
- Ventilation on the lower limit of normal, signs of peripheral obstruction. RV, TLC, and airways resistance are satisfactory.
- DL_{CO}sb: DL_{CO} 90%, DL_{CO}/V_A 86%.
- Transfer factor and transfer coefficient are within the normal range.

Radiology
- *Posteroanterior and lateral chest X-ray*: The lungs are expanded, and the parenchyma is without infiltrative changes. Vascular markings are adequate, the diaphragm is smooth, diaphragmatic angles are free. The size of the heart shadow is normal.
- *HRCT of the lungs*: The lung lobes present with an even distribution of multiple, small, oval, almost uniform, cystic formations with fine walls. The cysts affect the upper and lower lobes, including the costophrenic angles. Between the cysts, normal pulmonary parenchyma persists (Figs. 6.22a–d and 6.23).

6.4.1 Multidisciplinary Team and Differential Diagnosis

The HRCT of the lungs reveals multiple small cystic formations in a young woman with multiple renal angiomyolipomas. A history of epilepsy is reported. The findings are suggestive of tuberous sclerosis. It is suitable to complete the investigations with BAL, transbronchial biopsy (TBB) and an MRI scan of the brain.

Bronchoscopy, Bronchoalveolar Lavage and Transbronchial Biopsy (TBB)

- Macrophages 89%, lymphocytes 6%, neutrophils 4% and eosinophils 1%.
- Borderline levels of neutrophils and eosinophils, rarely present pigmentophages.
- TBB: The pulmonary parenchyma is mostly of normal configuration, however, in two small areas, there is an apparent smooth muscle proliferation within the septa with a hint of microcystic organisation.
- Conclusion: The findings are compatible with the clinical diagnosis of lymphangioleiomyomatosis.

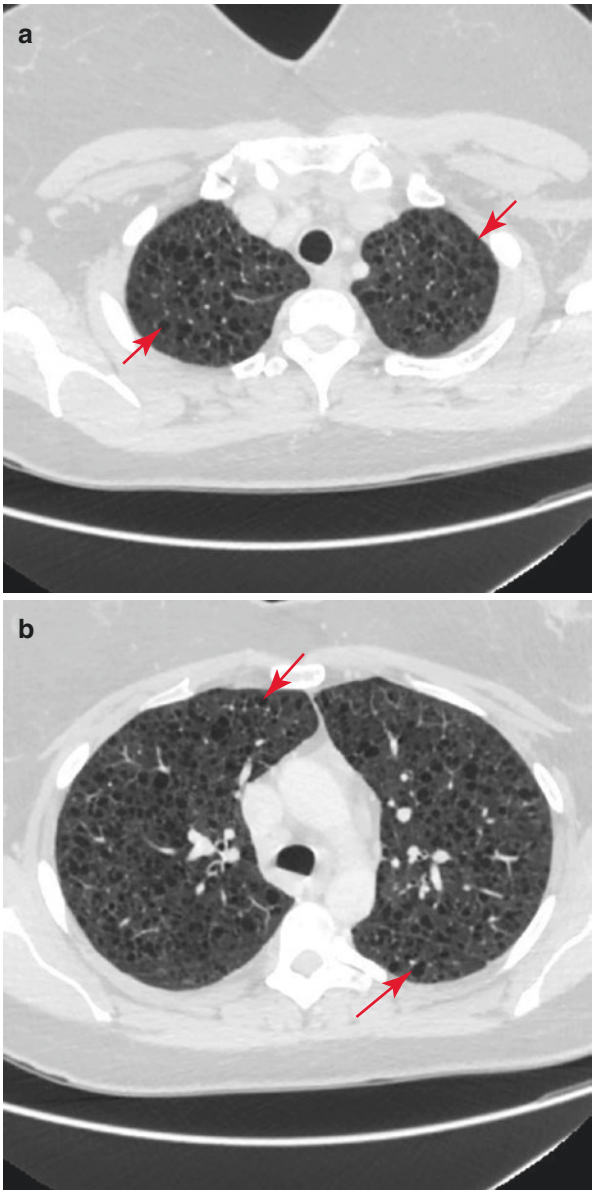
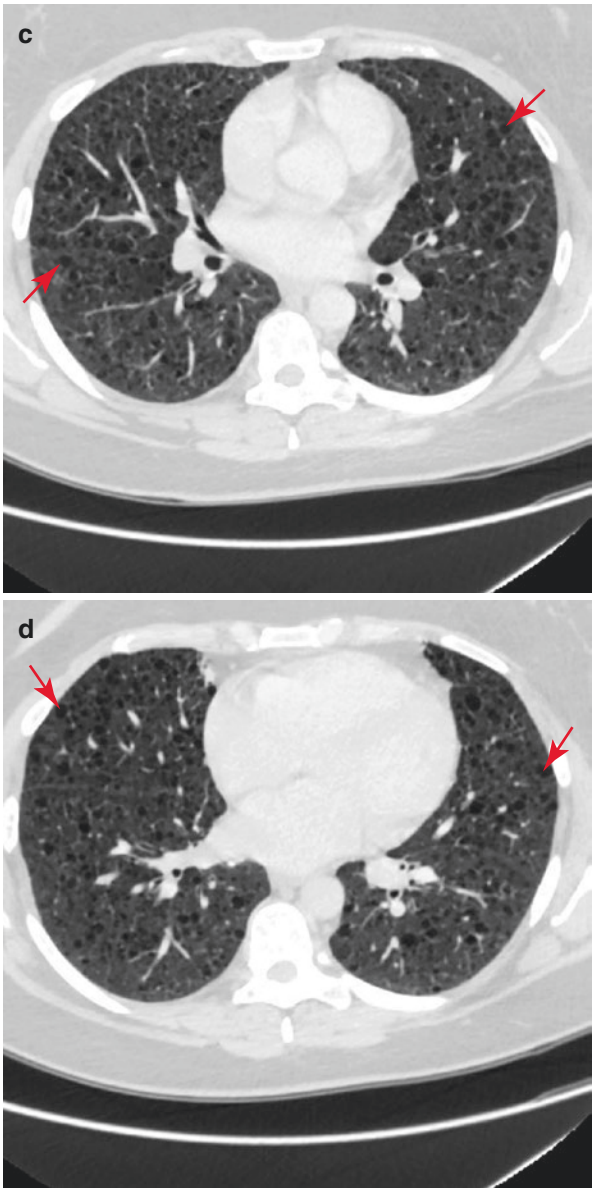


Fig. 6.22 (**a**–**d**) HRCT of the lungs: bilateral multiple small evenly distributed cysts with a fine wall

Fig. 6.22 (continued)



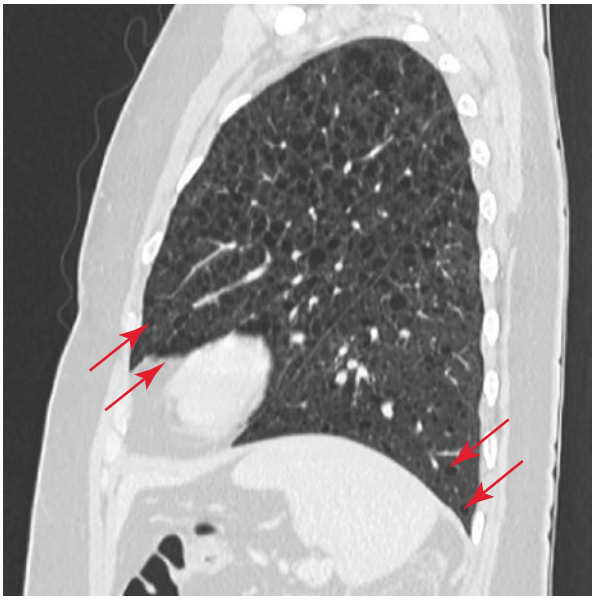


Fig. 6.23 HRCT of the lungs (sagittal reconstruction): cysts affecting upper and lower lobes, including costophrenic angles

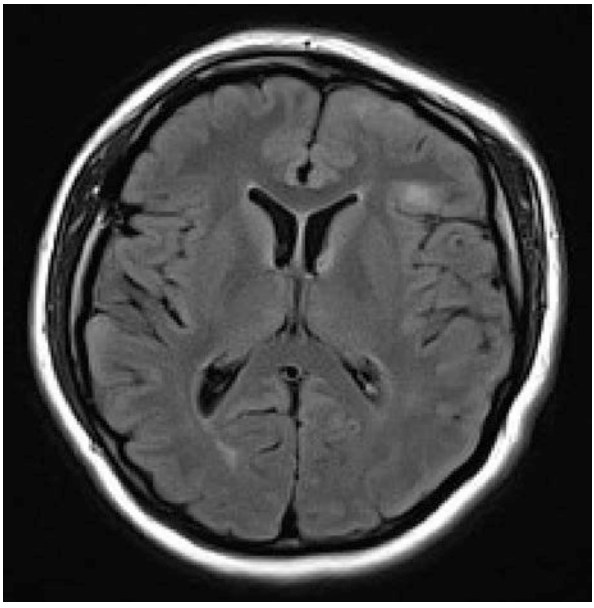


Fig. 6.24 MRI of the brain (FLAIR sequence in the axial plane): hypersignal regions on the left frontal-subcortical region and on the left adjacent to the left lateral ventricle in the subependymal zone

MRI of the Brain

- Fluid-attenuated inversion recovery (FLAIR) sequence identifies hypersignal areas visualised within the left frontal-subcortical region and concurrently on the left adjacent to the left lateral ventricle in the subependymal zone, characteristic of tuberous sclerosis (Fig. 6.24).

6.4.2 Conclusion

The findings were concluded as tuberous sclerosis with multiple organ disorders confirmed by molecular-genetic examination. So far, the patient refuses to consider lung transplantation.

Note
The finding of bilateral diffuse multiple small cystic formations with a fine wall in young women is suggestive of LAM, which may be part of tuberous sclerosis. The most common complications of LAM include pneumothorax and chylothorax.

6.4.3 Lymphangioleiomyomatosis—What We Should Consider in the Differential Diagnosis

1. Histiocytosis X: Unlike LAM, there are cysts of different sizes, irregular to bizarre shapes, which also have a thicker wall. Cysts predominate in the cranial and medial parts of the lungs—conserving bases and costophrenic angles. In the early stages of the disease, histiocytosis X can only be manifested by nodules. It occurs predominantly in young smokers (Fig. 6.25a, b).
2. Lymphocytic interstitial pneumonia (LIP): Cysts are less numerous compared to LAM and histiocytosis X and they predominate in the lower lobes. The wall of the cyst may be directly connected to the adjacent vessel. The cysts can be combined with GGO, and sometimes only nodules are the dominant pattern. Clinically, LIP usually is associated with Sjögren's syndrome, a connective tissue disease, or AIDS (Fig. 6.26a, b).

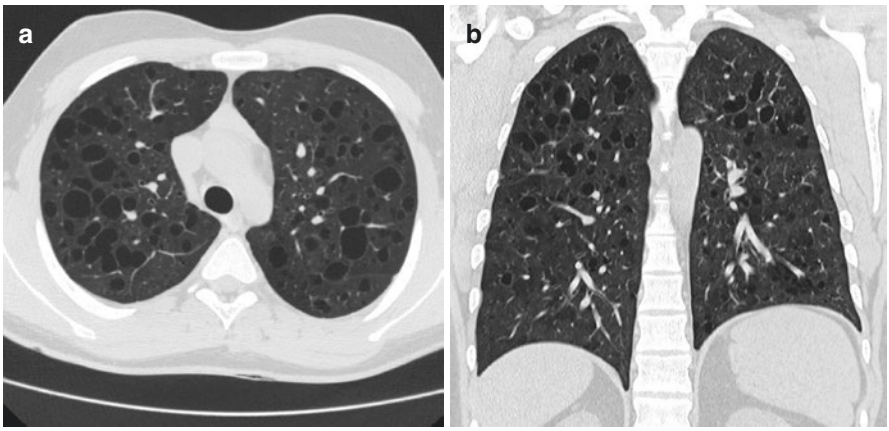


Fig. 6.25 (**a**) Histiocytosis X: thin-walled cysts of different sizes, irregular to bizarre shapes, predominate in the cranial and medial parts of the lungs. (**b**) Histiocytosis X (coronal reconstruction): cysts of different sizes, irregular to bizarre shapes, predominate in the cranial and medial parts of the lungs—conserving bases and costophrenic angles

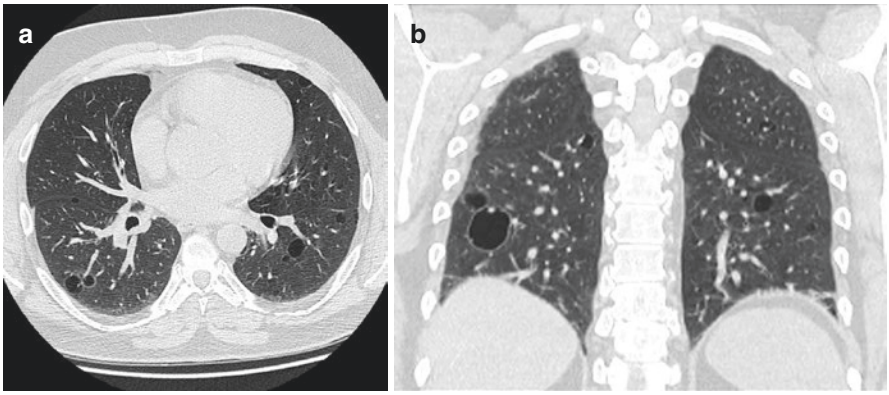


Fig. 6.26 (**a**) Lymphocytic interstitial pneumonia (LIP): GGO and cysts in the lower lobes. (**b**) Lymphocytic interstitial pneumonia (LIP), coronal reconstruction: cysts mainly in the lower lobes

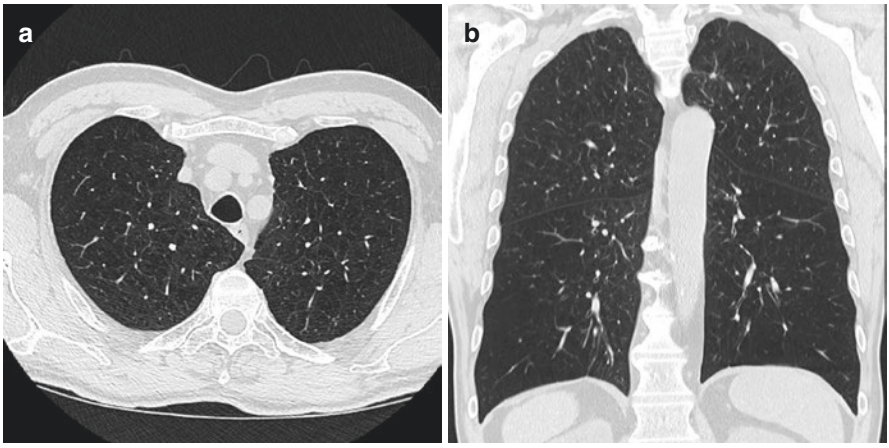


Fig. 6.27 (**a**) HRCT of the lungs: centrilobular emphysema. (**b**) HRCT of the lungs (coronal reconstruction): centrilobular emphysema

3. Centrilobular emphysema: At first glance on HRCT scans, the diffusely slightly heterogeneous structure of the pulmonary parenchyma is apparent, which is created by the predominant multiple hypodense regions. Unlike cysts, they do not have a wall. At the centre of these regions, there is a dotted centrilobular artery, which remains in apically and is often associated with other types of emphysema (paraseptal and bullous). It occurs in smokers (Fig. 6.27a, b).
4. Laryngotracheal papillomatosis: a rare cystic lung disease. Cysts are usually less numerous in comparison to LAM and Histiocytosis X. They can create various unusual to grotesque shapes, and these cysts can merge, creating solid forms. It is caused by human papillomavirus. It often affects the upper respiratory tract where it causes narrowing with corresponding symptoms (Fig. 6.28a, b).

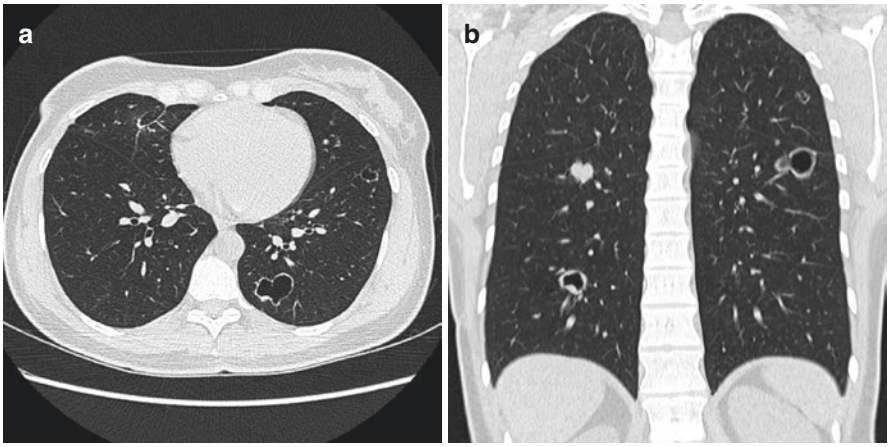


Fig. 6.28 (**a**) Laryngotracheal papillomatosis: Cysts with grotesque shapes. (**b**) Laryngotracheal papillomatosis, coronal reconstruction: cysts and nodules, cysts are with grotesque shape

6.5 Lymphocytic Interstitial Pneumonia

Martina Sterclova, Jana Votrubova, and Eva Kocova

Female, 67 years old.
Patient presents with progressing dyspnoea and a tickly cough.

Medical History

- Sjögren's syndrome for 5 years

Occupational History and Exposure

- Not significant
- Denies any use of abusive substances, non-smoker
- Medication history—uses only artificial tears, occasionally non-steroidal anti-inflammatory drugs

History of Present Compliant

- Breathlessness in the last year, feels like she cannot fully breathe in, with difficulties walking up one floor. At the same time has a worsening persistent dry cough, fatigue and occasionally higher body temperature. The patient continues to have dryness of the mucous membranes, eyes, and progressing tooth decay.

Objective Finding

- Findings are normal including vesicular breathing, without secondary phenomena.

Examination

Lung Functional Tests

- FVC 2.54 L/86% (ref. v), VC 2.76 L/94% (ref. v), FEV_1 1.84 L/74% (ref. v), Tiff. 65%, TLC 6.25 L/115% (ref. v), RV 3.48 L/165% (ref. v), DL_{CO} 6.23 mmol/kPa/min/68% (ref. v)
- Mild obstructive ventilatory disorder with slight pulmonary hyperinflation, and marginally reduced transfer factor for CO

Radiology

- *Posteroanterior chest X-ray*: Bilateral basal cystic translucency, with a thin wall (Fig. 6.29).
- *HRCT of the lungs*: Bilateral multiple thin-walled cystic formations. The apexes of the lungs are spared. The cystic formations are increasing craniocaudally, and are present in the posterior costophrenic angles. The cysts are located mainly perivascularly and subpleurally (Figs. 6.30a–d and 6.31).

Auxiliary and Laboratory Examinations

- Rheumatological examination: this is a typical image of primary Sjögren's syndrome, without signs of a systemic connective tissue disease.

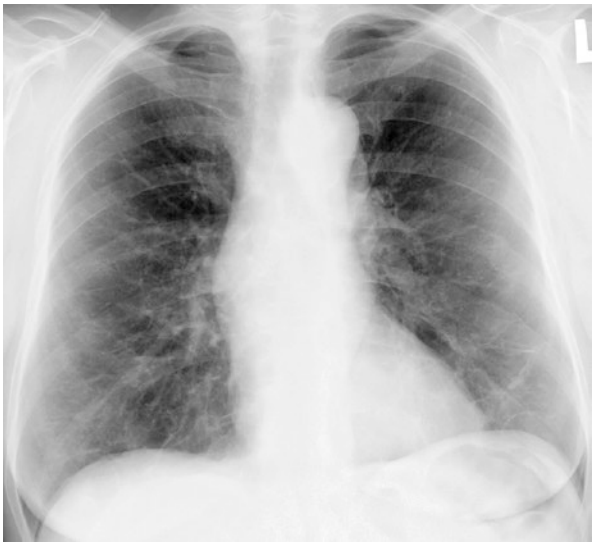


Fig. 6.29 Posteroanterior chest X-ray: bilateral basal cystic lucency with thin wall

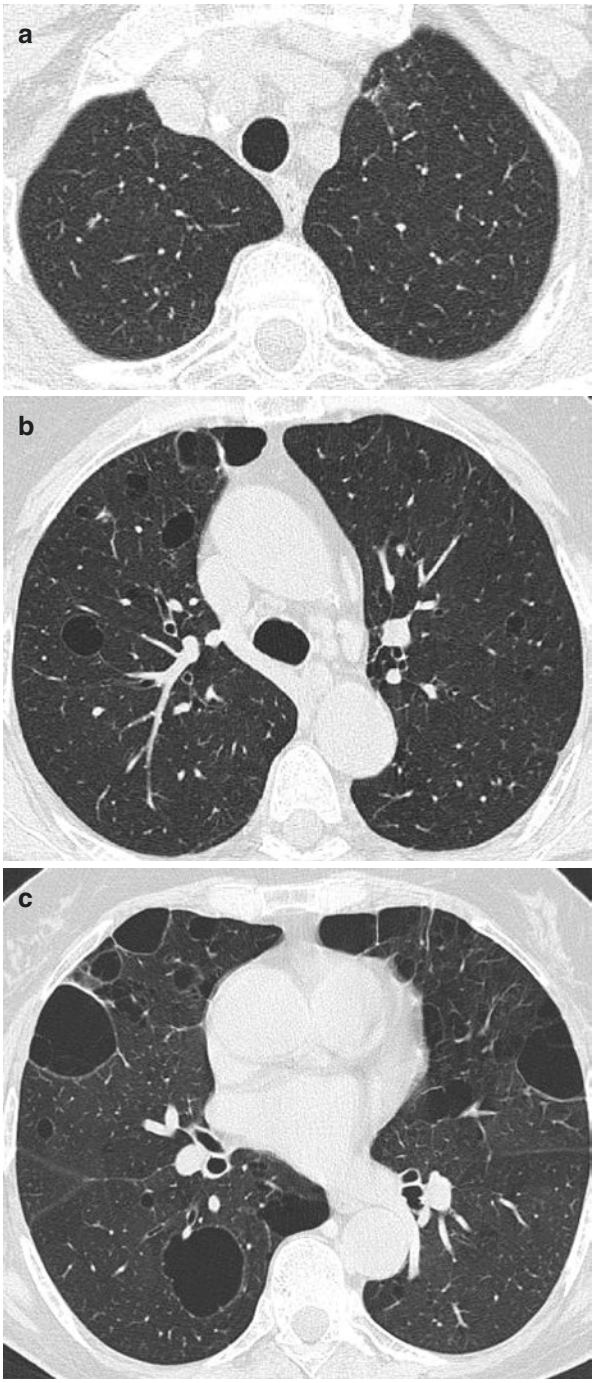


Fig. 6.30 (**a**) HRCT of the lungs: apexes of the lungs with normal findings. (**b**) HRCT of the lungs (the same patient, scan above carina): bilateral cystic formations. (**c**) HRCT of the lungs: bilateral multiple cystic formations distributed within the perivascular and subpleural area. (**d**) HRCT of the lungs: bilateral multiple cystic formations distributed within the perivascular and subpleural area, also affected the costophrenic angles

Fig. 6.30 (continued)

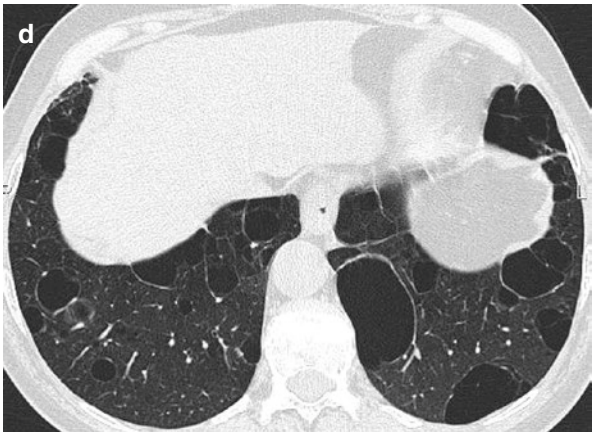
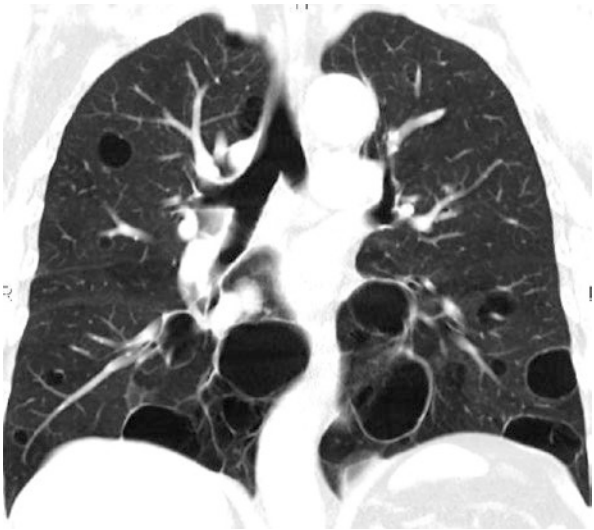


Fig. 6.31 HRCT of the lungs, coronal reconstruction: multiple cysts with maximum predilection to the lower lobes



- Allergological and immunological examinations: without evidence of immunodeficiency or allergy.
- Haematological examination: included a sternal puncture, without any major abnormalities.
- Ophthalmological examination: a positive Schirmer test, and xerophthalmia.
- Laboratory tests: no pathological findings, with a low indication of inflammation. HIV and EBV infections were not identified.

6.5.1 Multidisciplinary Team and Differential Diagnosis

This is presentation of multi-cystic lung disease without nodule formations. The patient was detected positive for Sjögren's syndrome by a rheumatologist. Repeatedly, no proof of infection was found.

The conclusion of the MDT: Radiologically, signs of lymphocytic interstitial pneumonia. Bronchoalveolar lavage and transbronchial biopsy were recommended.

Bronchoscopy, Bronchoalveolar Lavage and Transbronchial Biopsy

- Endobronchial findings were normal.
- BAL: 62% alveolar macrophages, 29% lymphocytes, 9% neutrophils, and rare eosinophils. An immunophenotyping assessment was without evidence of clonality. Staining of CD1a and S-100 was negative, and there were no signs of infection.
- TBB: Findings are compatible with lymphocytic pneumonitis, clonality not proven.

6.5.2 Conclusion

According to HRCT and the BAL and TBB findings, the diagnosis was finalised as lymphocytic interstitial pneumonia in Sjögren's syndrome**.** Infectious aetiology and haematological malignancy have not been identified.

Note
Lymphocytic interstitial pneumonia is a disease often associated with Sjögren's syndrome, in other autoimmune diseases and within infections (HIV, EBV, and HTLV). On HRCT, it typically presents with thin-walled cysts in a perilymphatic and subpleural distribution, predominantly in the lower lobes, sometimes with spotted GGO within the upper lobes. Differential diagnostics of HRCT diagnostics in cystic lung diseases is based on the identification of cystic distribution, the presence of cyst walls and the coincidence with other patterns.

6.5.3 Lymphocytic Interstitial Pneumonia—What We Should Consider in the Differential Diagnosis

1. Lymphangioleiomyomatosis: Regular cysts affecting whole lungs including the posterior costophrenic angles (Fig. 6.32).
2. Centrilobular pulmonary emphysema: 'Holes' without walls, at the centre of which is a dotted density—centrilobular artery (Fig. 6.33).
3. Pulmonary Langerhans Cell Histiocytosis: A pulmonary disease with centrilobular nodules that can cavitate. At a later stage, it presents as a cystic lung disorder with bizarre cysts that are typically not in the posterior costophrenic angles (Fig. 6.34).
4. Bullous emphysema: Paraseptal emphysema with subpleural cysts larger than 1 cm, typically in the upper lobes in smokers (Fig. 6.35).

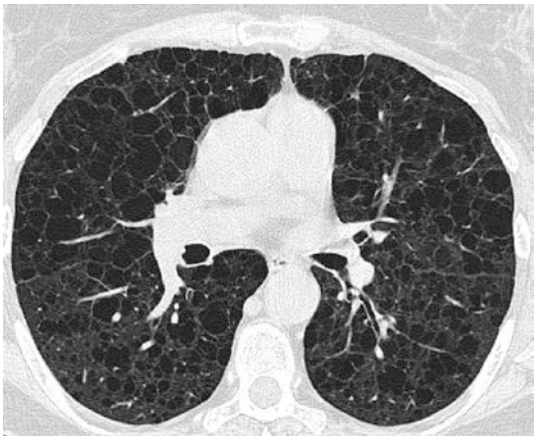


Fig. 6.32 Lymphangioleiomyomatosis: Regular cysts affecting whole lungs

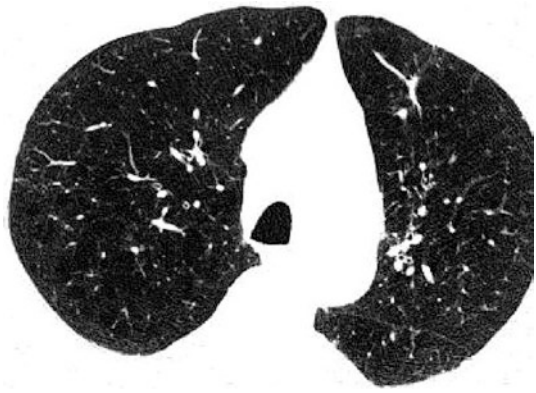


Fig. 6.33 Centrilobular pulmonary emphysema: 'Holes' without walls, at the centre of which is a dotted density—centrilobular artery

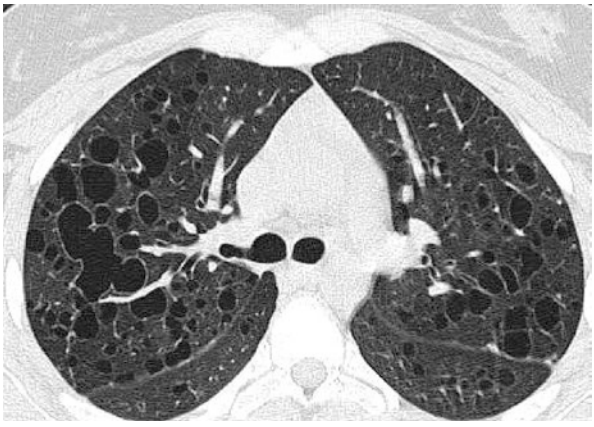


Fig. 6.34 Pulmonary Langerhans Cell Histiocytosis: multiple cysts with bizarre shape

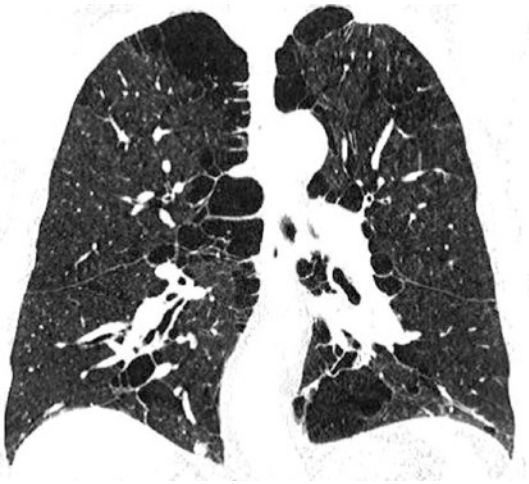


Fig. 6.35 Paraseptal emphysema with subpleural cysts larger than 1 cm

6.6 Syndrome of Combined Fibrosis and Emphysema

Martina Sterclova, Jana Votrubova, and Eva Kocova

Female, 60 years old.
Presents with exertional dyspnoea, dry cough and stabbing pains behind the sternum.

Medical History
No significant past medical issues, healthy.

Occupational History and Exposure

- The patient works in garages with increased exposure to dust. She is a lifelong non-smoker, with no history of passive smoking. Lives in a flat, which has a dry environment, and owns a dog (used to have a cat). She does not have birds as pets and does not use a swimming pool or a whirlpool.

History of Present Compliant

- For about 10–12 years, she observes that she is quicker to become short of breath compared to her peers. She has been having a slight dry cough for 2 years. After coughing, she tends to have a strong pain in the chest behind the sternum, bound to breathing exertions.

Objective Finding

- Vesicular breathing, bilateral basal crepitations, nail clubbing is not present.

Examination

Lung Functional Tests

- FVC 2.89 L/97% (ref. v), VC_{max} 3.12 L/105% NH, TLC 5.04 L/95% (ref. v), DL_{CO} 3.55 mmol/kPa/min/44% (ref. v).
- Vital capacity is in the normal range and is without a restrictive ventilation disorder. The transfer factor is moderate to severely decreased, mostly due to the loss of alveoli.

Radiology

- *Posteroanterior and lateral chest X-ray*: At first glance, there is a pathological transparency in both lungs with an alternation of hypo- and hyper-transparent zones. The finding is very well evident in the lateral projection in the retrocardiac space, where the hyperinflation of the basal segments of the lower lung lobes is noticeable (Fig. 6.36a, b).
- *HRCT of the chest*: A combination of emphysema, predominantly in the upper lobes, and fibrosis, predominantly in the lower lobes. The advanced stage of the disease is characterised by honeycombing, reticular opacities and traction bronchiectasis (Fig. 6.37a–e).

Bronchoalveolar Lavage

- Alveolar macrophages 51%, neutrophils 15%, lymphocytes 26%, and eosinophils 8%.

Auxiliary and Laboratory Examinations

- ANA neg., ENA neg., anti-dsDNA neg., ANCA neg., RF neg., values of specific IgG against mould max. 53 mg/L, other values (mites, feathers, bacteria, isocyanates, animal hair) up to 20 mg/L, A1AT in the standard range.

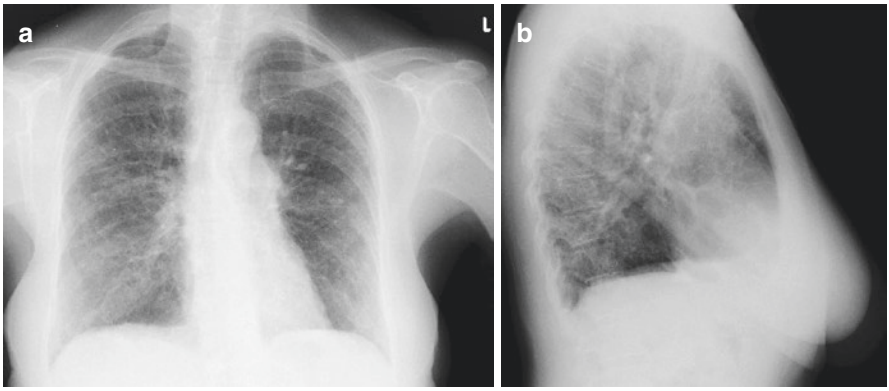


Fig. 6.36 (**a**) Posteroanterior chest X-ray: reticulation, patchy areas of increased and decreased transparency of the lung parenchyma. (**b**) Lateral chest X-ray: reticulation, areas of increased and decreased transparency of the lung parenchyma

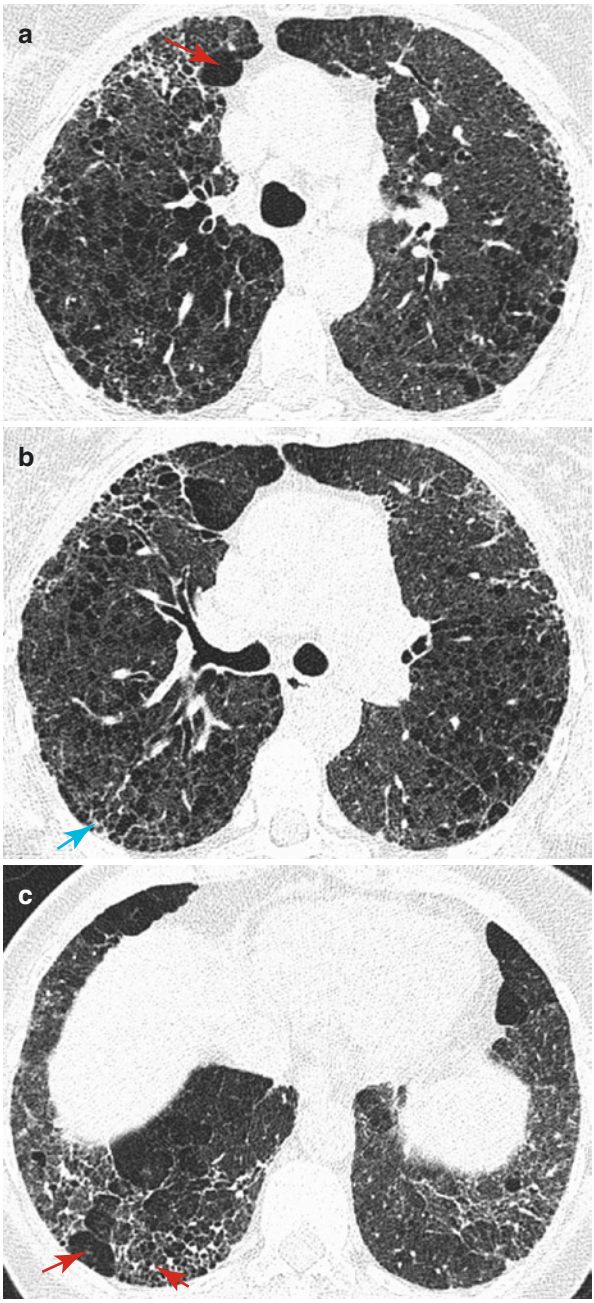


Fig. 6.37 (**a**, **b**) HRCT of the chest: a combination of emphysema in the upper lobes, and reticulations subpleurally. (**c**) HRCT of the chest: reticulations, traction bronchiectasis, with honeycombing. (**d**) HRCT of the chest (coronal reconstruction): a combination of emphysema predominantly in the upper lobes, and especially subpleural reticulation, and basally signs of fibrosis with a decreased volume of the lower lobes, traction bronchiectasis, and honeycombing. (**e**) HRCT of the chest (sagittal reconstruction): a combination of emphysema predominantly in the upper lobes, and especially subpleural reticulation, and basally signs of fibrosis with a decreased volume of the lower lobes—shift of the main fissure caudally, traction bronchiectasis, and honeycombing

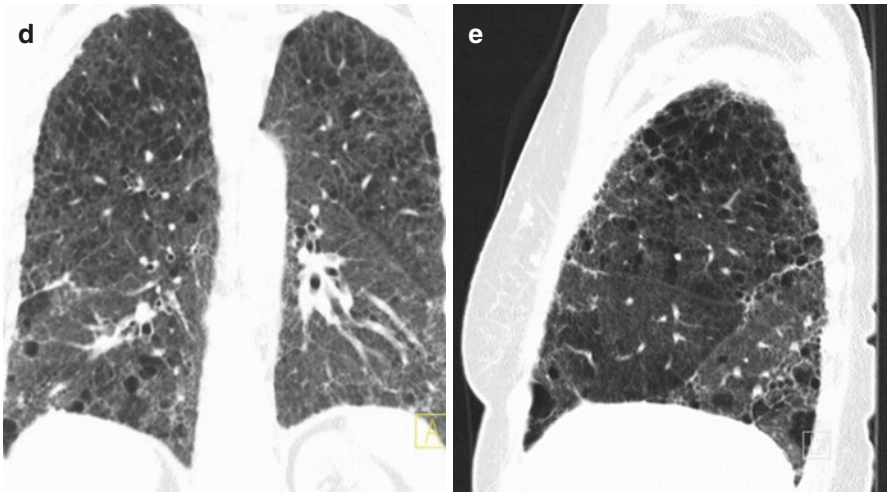


Fig. 6.37 (continued)

Spiroergometry

- There was a slightly reduced exercise tolerance, and the test was terminated due to dyspnoea. The circulatory response was at the limit of the standard, with reduced cardiac output dynamics. Ventricular function appears to be borderline, with a mild increase in the ventilatory response due to dead space ventilation, which is partially declining. There was no mechanical limitation. The oxygenation was in slow decline with a moderate chance of pulmonary hypertension. The findings correspond with the clinical diagnosis. The results show affliction of respiratory, rather than a mechanical, dysfunction of the lungs.

6.6.1 Multidisciplinary Team and Differential Diagnosis

The patient is suspected to have an ILD and is indicated for VATS and histological verification.

VATS and Histology

One sample from the right lower lobe. Diagnostically of no value as it was from the area of advanced changes corresponding to the end-stage pulmonary fibrosis. This histologic sample did not clarify the aetiology of the disease. Diagnostically specific changes corresponding with UIP patterns were not present.

6.6.2 Second Multidisciplinary Consultation with Diagnostical Reasoning

The patient has an ILD, surgical pulmonary biopsy from one lobe exposed signs of nonspecific end-stage fibrosis. CT scan signs of emphysema and fibrosis. Bronchoalveolar lavage suspicious of hypersensitivity pneumonitis combined with pulmonary fibrosis and emphysema (CPFE).

6.6.3 Conclusion

This is likely a case of HP with a radiological signs CPFE, with histologically confirmed advanced end-stage pulmonary fibrosis. The ambiguous high percentage of lymphocytes in BAL may be due to a source of inhaled antigens.

A therapeutic trial of systemic corticosteroids was initiated.

6.6.3.1 CPFE Syndrome

The term CPFE was first introduced in 2005 by Cottin et al. The group described patients with a combination of emphysema and an ILD of unknown aetiology, with dominant fibrosis of the lower pulmonary lobes. Similar radiological signs can also be found in patients with known exposures to organic inhaled antigens (especially smokers with farmer's lung), or in patients with a systemic connective tissue disease (most commonly patients with rheumatoid arthritis or systemic scleroderma, often with a history of nicotinism). If the syndrome is manifested in a lifelong nonsmoker, a genetic cause of the disease can also be considered. The CPFE can be found in patients with a genetic mutation in surfactant protein C and in patients with a mutation in protein ABCA3, a storage protein of surfactant in the lamellar bodies of alveolar epithelia of type 2 cells.

In these patients, it is necessary to interpret carefully data obtained by a simple spirometry testing without forgetting to test the transfer factor. The combination of fibrotic changes and emphysema can paradoxically sufficient vital capacity (despite the fact that the patient usually complains of severe exertional dyspnoea), and the patient may be erroneously misdiagnosed. As a rule, we see the reduction of the transfer factor.

Emphysema is usually dominant in the upper pulmonary lobes and is in centrilobular or paraseptal zones. Fibrosis is predominant basally. The most common is the radiological sign of UIP, but signs consistent with NSIP, DIP, or even RB-ILD may be encountered.

Patients with CPFE are more likely to have pulmonary hypertension than patients with IPF or COPD. Guidelines on how to proceed in cases of pulmonary hypertension in CPFE are not available.

Note
In patients with a radiological CPFE image, autoimmune diseases are often the primary cause, and should be actively considered. In young non-smokers with a CPFE presentation, it is appropriate to exclude genetic causes of the disease and familial interstitial pneumonitis. A complete functional examination is necessary, and never should the severity of the disability be assessed solely on the basis of a simple spirometry.

6.6.4 Combined Pulmonary Emphysema and Fibrosis Syndrome—What We Should Consider in the Differential Diagnosis

1. Idiopathic pulmonary fibrosis: Signs of usual interstitial pneumonia—with dominant fibrosis, and possible minimal pulmonary emphysema changes (Fig. 6.38).
2. Systemic connective tissue disease with lung disease: Such as in rheumatoid arthritis and systemic scleroderma—thickened interlobular septa, GGO, and signs of fibrosis. Pulmonary emphysema is not present. There is a history of systemic disease (Fig. 6.39).
3. Familial interstitial pneumonitis: Subpleural pulmonary reticulation, and bronchiectasis. HRCT signs are not specific (Fig. 6.40).

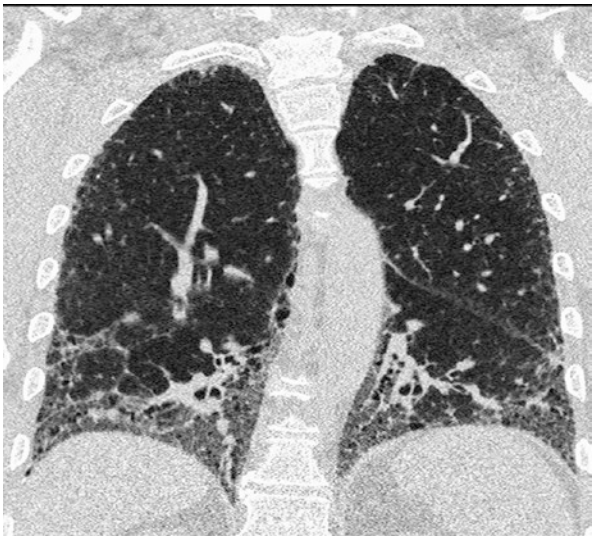


Fig. 6.38 Idiopathic pulmonary fibrosis: Signs of usual interstitial pneumonia—honeycombing, traction bronchiectasis, reticulations, GGO within the reticulations, and possible minimal lung emphysema

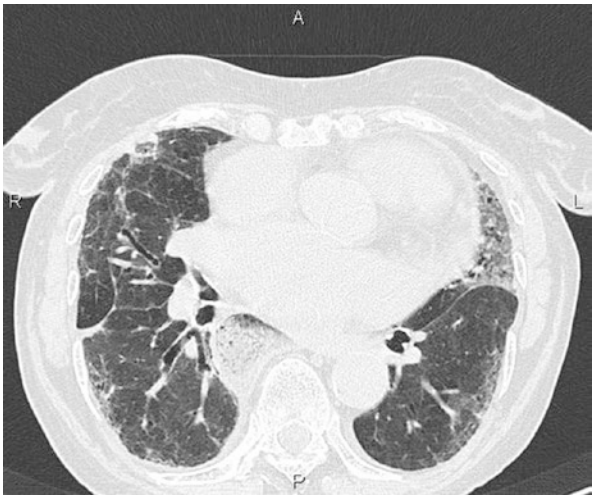


Fig. 6.39 HRCT of the lungs in patient with systemic sclerosis—thickened interlobular septa, GGO, and signs of fibrosis. Pulmonary emphysema is not present. Dilated oesophagus

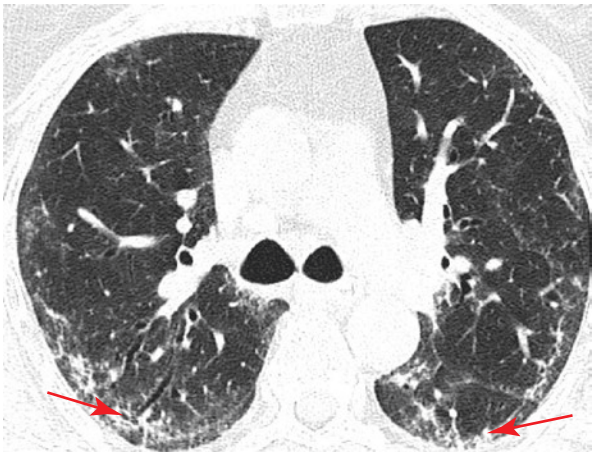


Fig. 6.40 HRCT of the lung of the patient with Familial interstitial pneumonitis: Subpleural pulmonary reticulation, and bronchiectasis

Further Reading

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Linear Opacities

7

Eva Kocova, Vladimir Bartos, Martina Sterclova, Jana Votrubova, Filip Ctvrtlik, Monika Zurkova, and Vladimíra Lostakova

7.1 Non-specific Interstitial Pneumonia

Eva Kocova and Vladimir Bartos

In the last 3 months, she had difficulties to take a deep breath at exertion, and had a dry cough.

Medical History

- None significant, not on long-term medication

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_7

Occupational History and Exposure

- Medical doctor, without occupational exposures
- Lives with family in a block of flats, without pets
- Social history: From the age of 20 to 62 years, smoked 2 cigarettes a day

History of Present Compliant

- Over the last 3 months, she has been feeling as if she is unable to breathe in fully during exertion. Has a dry non-productive cough. The patient presents without joint symptomatology or manifestations of systemic connective tissue disease.

Objective Finding

- Vesicular breathing, with bi-basal crepitations. Clubbing of the nails is not present. Otherwise physiological findings.

Examination

Lung Functional Tests

- VC 4.34 L/133% (ref. v), FEV_1 3.27 L/117% (ref. v), Tiff. 75%, TLC 5.76 L/103% (ref. v), DL_{CO} 67% (ref. v).
- Normal parameters of ventilation (without an obstructive or restrictive ventilation disorder), and a mild limited pulmonary diffusion for CO.

Radiology

- *Posteroanterior chest X-ray*: The image is not in full inspiration, and the diaphragm is raised, particularly the left cupola. The pulmonary parenchyma appears without pathological changes.
- *HRCT of the lungs*: Bilateral subpleural GGO with subpleural sparing. Changes are expressed craniocaudally. There are no signs of fibrosis (Fig. 7.1a–c).

7.1.1 Multidisciplinary Team and Differential Diagnosis

Signs on HRCT are compatible with non-specific interstitial pneumonitis (NSIP). Subpleural dense opacities with a typical strip of subpleural sparing are seen. The changes are increasing in the caudal direction. There are no signs of fibrosis, neither a reduction in pulmonary volume. Both, traction bronchiectasis and honeycombing are not present.

Systemic connective tissue disorders were excluded by the rheumatologist. Autoantibodies and immunodeficiency are not verified.

The conclusion of the MDT: Clinically and radiologically, this is undoubtedly a non-specific interstitial pneumonia. The team recommended additional bronchoalveolar lavage and transbronchial pulmonary biopsy to be performed (cryobiopsy was not available at that time, and the patient refused VATS biopsy).

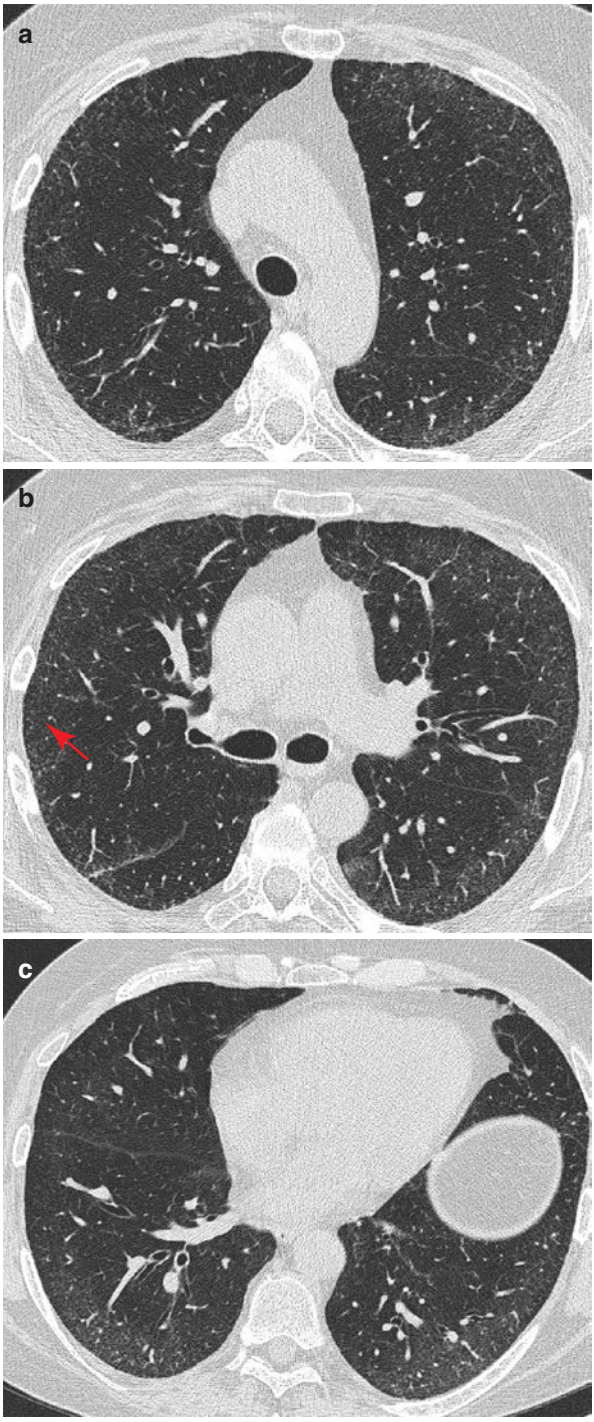


Fig. 7.1 (**a**) HRCT of the lungs: subpleural reticulations and GGO. Subpleural sparing is evident. (**b**) HRCT of the lungs: more subpleural reticulations and GGO. Note subpleural sparing—continued in the craniocaudal direction. (**c**) HRCT of the lungs: subpleural reticulations and GGO expressed in a craniocaudal gradient, with no honeycombing. Note subpleural sparing—continuation in the craniocaudal direction

Bronchoscopy, Bronchoalveolar Lavage and TBB

- BAL: 73% macrophages, 20% lymphocytes with a slight predominance of CD8+, 6% neutrophils and 1% basophils.
- TBLB: non-diagnostic.

7.1.2 Conclusion

The presentation appears to be non-specific interstitial pneumonia, in most likely an idiopathic form of the disease. Corticoid therapy was initiated, which was very difficult for the patient to tolerate due to muscle weakness (without objective correlation) and psychological decompensation.

Several aplastic anaemia with pancytopenia developed after several months of treatment. There was a need of antithymocyte globulin therapy, followed by cyclophosphamide to stabilise the haematological complications. Over the years, the patient developed Sicca syndrome and Raynaud's phenomenon, as well as persisting myopathic issues. However, according to a joint opinion of a rheumatologist, neurologist, and haematologist, this was not a typical development of SCTD. Over the years, the patient's pulmonary function decline, and the disease progressed on lung HRCT (Fig. 7.2). The possibilities of combined immunosuppressive therapy were very limited by the patient's comorbidities. After 5 years of treatment, the patient developed a restrictive ventilatory defect, severe disability of pulmonary diffusion for CO, and developed respiratory insufficiency with the need for long-term home oxygen therapy. Eight years after the diagnosis, the patient died of respiratory failure.

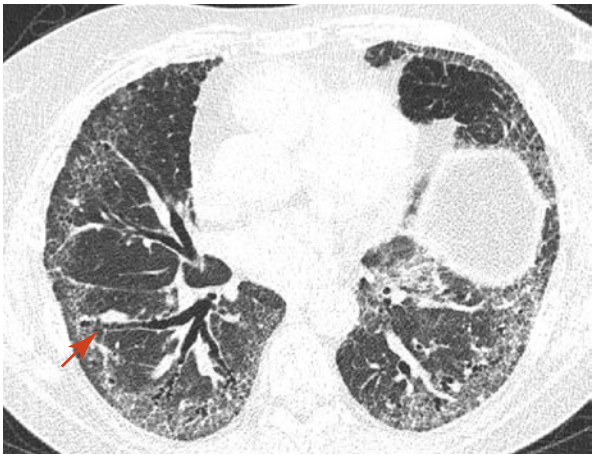


Fig. 7.2 HRCT of the lungs seven years' post-diagnosis: slow progression noted over time, with the development of fibrotic changes with traction bronchiectasis, progression of reticulations and GGO, without honeycombing. Subpleural sparing is notable

7.1.3 Non-specific Interstitial Pneumonia

Non-specific interstitial pneumonia is characterised by the presence of bilateral subpleural ground glass opacities, typically with subpleural sparing. In later stages, fibrosis with traction bronchiectasis or honeycombing may develop.

Note

- Non-specific interstitial pneumonia is an idiopathic interstitial disease. The NSIP picture may be found in SCTD, a drug-induced pulmonary disorder, HP, etc. Detailed history and rheumatological screening are an essential part of the diagnosis of NSIP.
- Sometimes patients with NSIP do not meet the rheumatological criteria for SCTD, but may have symptoms indicating an autoimmune origin of the disease.

7.1.4 Non-specific Interstitial Pneumonia—What We Should Consider in the Differential Diagnosis

1. Drug-induced lung disorder: A history of the use of medication which may have adverse effects on the lungs—refer to www.pneumotox.com (Fig. 7.3).
2. Chronic Hypersensitivity Pneumonitis: Suspected or proven exposure to organic antigens, with fibrosis on a CT scan, air trapping, and centrilobular nodules (Fig. 7.4).
3. Usual interstitial pneumonia (UIP): GGO is more prevalent in NSIP and in NSIP there is typical subpleural sparing (Fig. 7.5).
4. Non-specific interstitial pneumonia in systemic connective tissue disease: Most common in cases of rheumatoid arthritis, systemic scleroderma, or Sjögren's syndrome. Often, the development of the systemic connective tissue disease may precede pulmonary findings (Fig. 7.6).

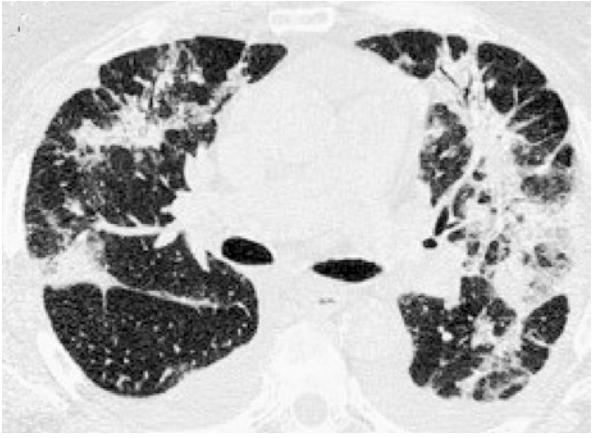


Fig. 7.3 Drug-induced lung disease: Patchy non-regular consolidations

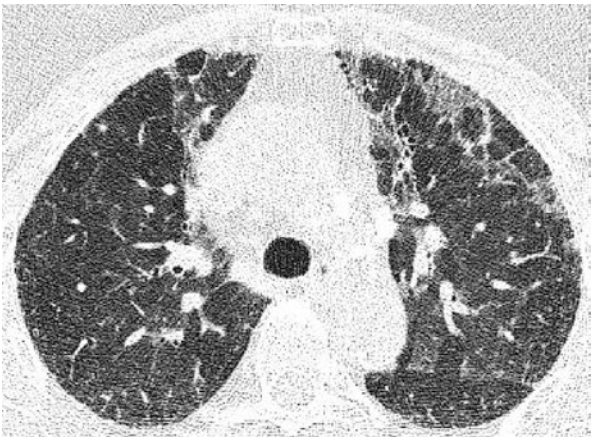


Fig. 7.4 Chronic Hypersensitivity Pneumonitis: Reticulations and GGO "head cheese sign"

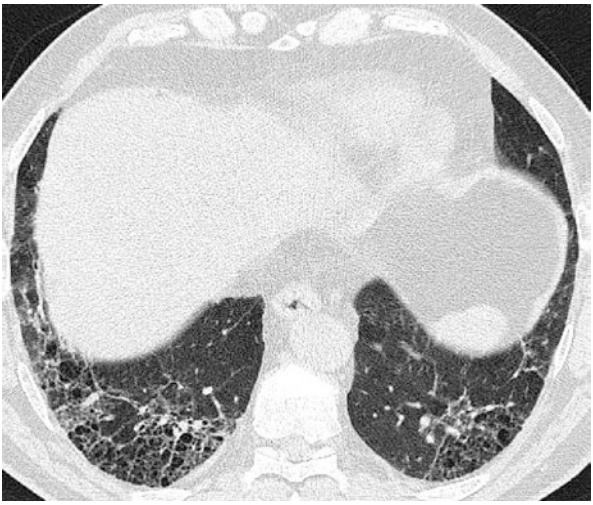


Fig. 7.5 Idiopathic interstitial pneumonia: honeycombing and reticulations in basal parts of the lungs

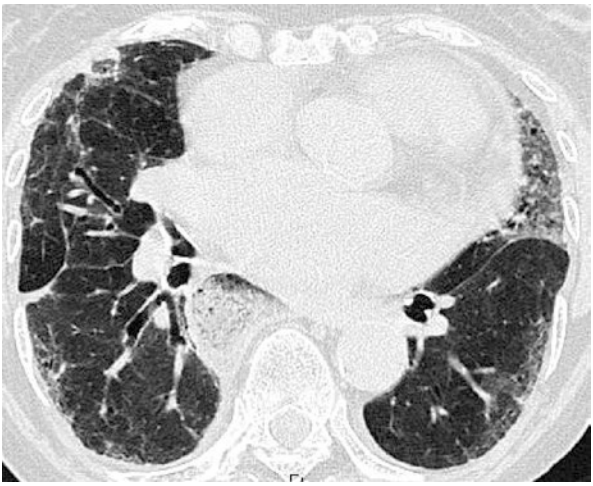


Fig. 7.6 HRCT of the lung of the patient with systemic scleroderma: reticulations and GGO, dilated oesophagus

7.2 Non-specific Interstitial Pneumonia II

Martina Sterclova, Jana Votrubova, and Eva Kocova

Male, 56 years old.
The patient presents with a 6-month history of persisting cough with the production of white phlegm.

Medical History

- Intermittent asthma and allergic rhinoconjunctivitis (spring pollen and grass)
- Ischemic heart disease, recurrent history of myocardial infarction (three in total, the last one was 5 years ago)
- History of hepatitis C (10 years ago, the patient was treated for 5 years with ribavirin, interferon alpha, PEGylated interferon alpha-2b, PEGylated interferon alpha-2a)
- Dyslipidaemia
- History of deep vein thrombosis of the right lower leg
- Ten years ago, he had an episode of pancolitis, treated with mesalamine at times of coming attacks

Occupational History and Exposure

- Electrician (previously worked as a diesel generator operator)
- Lives with family, with no pets, does not use a whirlpool
- Smoking history: from 20 to 40 years of age smoked ten cigarettes daily, since 40 he has been smoking occasionally
- Medications: cetirizine, omeprazole, ramipril, atorvastatin, acetylsalicylic acid, salbutamol (on an as required regime), mesalamine as needed

History of Presenting Compliant

- The patient complains of a 6-month lasting productive cough with white sputum production, practically every day. He has observed exertional dyspnoea since his first heart attack. He can climb 284 stairs, the dyspnoea does not significantly progress, and he does not present with any chest pain.

Objective Finding

- Vesicular breathing, basal crepitations, and nail clubbing.

Examination

Lung Functional Tests

- FVC 4.83 L/79% (ref. v), VC_{max} 4.83 L/84% (ref. v), TLC 6.27 L/73% (ref. v), DL_{CO} 3.91/32% (ref. v)
- A slight decrease in the forced vital capacity, and the resting maximal capacity is within the standard range. It is indicative of a slight restrictive ventilatory disorder. Severe transfer factor failure mainly due to alveolar loss and a ventilation/perfusion imbalance

Radiology

- *Posteroanterior and lateral chest X-ray*: A very fine accentuation of pulmonary markings identified, with bilateral pulmonary hilar enlargement. Widening of the cardiac shadow in both directions (Fig. 7.7a, b).
- *HRCT of the lungs*: GGO, especially subpleurally, reticulation, with basal traction bronchiectasis (Fig. 7.8a–c).

Bronchoalveolar Lavage

- Significantly cellular, unclear samples, with multiples of eosinophils at the edges and numerous neutrophils.

Autoimmunity Screen

- A highly positive RF of the IgA class, slightly elevated RF of the IgG class, ANA negative, ENA negative, ANCA negative and anti-dsDNA negative. aCCP was not examined.

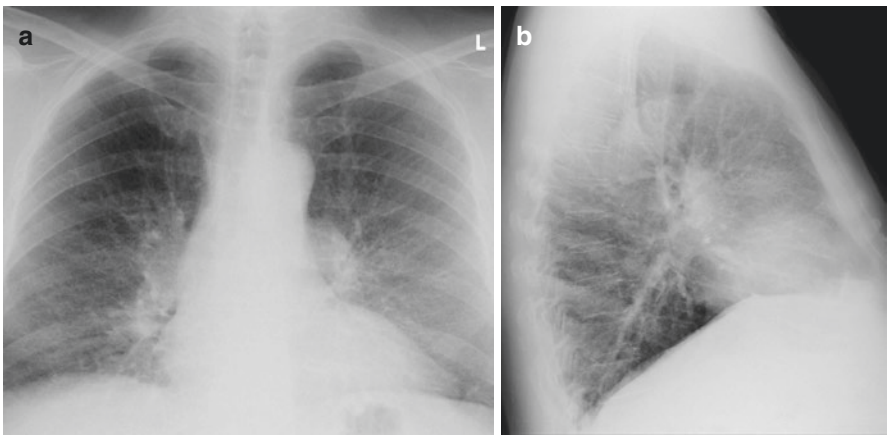


Fig. 7.7 (**a**) Posteroanterior and chest X-ray: very fine accentation of pulmonary markings, bilateral enlargement of the pulmonary hilar, widening of the cardiac shadow in both directions. (**b**) Lateral chest X-ray: very fine accentation of pulmonary markings

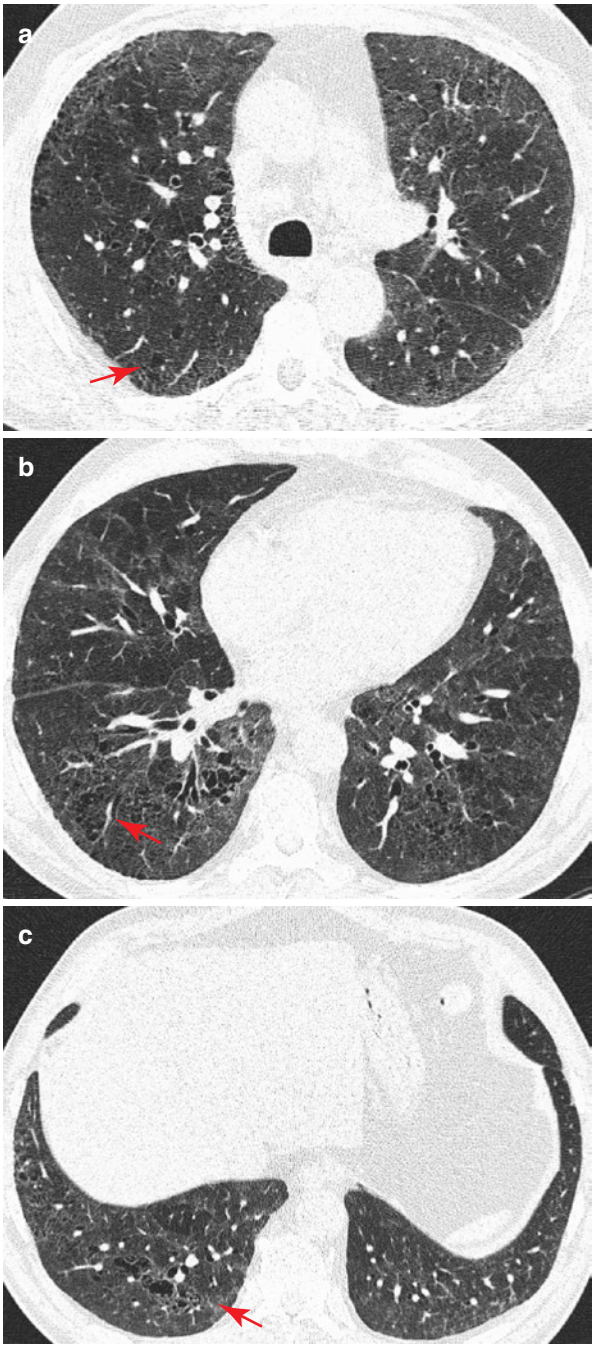


Fig. 7.8 (**a**) HRCT of the lungs: fine subpleural reticulations in combination with GGO. (**b**) HRCT of the lungs: fine subpleural reticulations in combination with GGO and moderate bronchiectasis. (**c**) HRCT of the lungs: fine subpleural reticulations in combination with GGO and bronchiectasis

7.2.1 Multidisciplinary Team and Differential Diagnosis

Within the mediastinum, there are multiple and enlarged lymph nodes, subpleural bullae within in the upper lobes, GGO, and traction bronchiectasis. This is probably an active fibrosing interstitial lung disease, being the first manifestation of rheumatoid arthritis (so far, the patient was still without clinical manifestations). The patient was not capable of micromorphological verification at the time of MDT. It was recommended to perform spiroergometry and to exclude hepatic cirrhosis, which may lead to the development of the hepatopulmonary syndrome.

Spiroergometry

- The tolerance load was moderately decreased. However, the circulatory response was adequate with a good cardiac output dynamics. The ventilation response was mild to moderately elevated with higher ventilation and perfusion ratio, which decreases only partially. There are signs of a slight mechanical limitation of ventilation, as oxygenation is significantly decreased. The overall physical condition was weak, and the probability of pulmonary hypertension was low. The findings correspond to the clinical diagnosis of ILD, and concomitant hepatopulmonary syndrome is unlikely.

Liver Investigations and Transient Elastography

- After successful treatment of the HCV infection, the identified liver fibrosis was minimal and most likely not associated with the lung damage. HCV was successfully eradicated. The liver stiffness corresponds to the fibrosis. Significant steatosis was present.

Rheumatological Examination

- The patient was with a negative medical history and without joint pathology, rheumatoid arthritis was states as highly unlikely.

7.2.2 Conclusion

Patient with a non-specific interstitial pneumonia (fibrous form). Combined immunosuppressive therapy was initiated: systemic corticosteroids and azathioprine.

7.2.3 Non-specific Interstitial Pneumonia

The term non-specific interstitial pneumonia was first used in 1994, and for many years it has been understood as a sort of an “intermediate storage,” for groups of patients for whom we anticipate further development of their disease, until their

disease can be clearly defined. Since 2008, the following criteria have been used to diagnose NSIP:

- Dyspnoea and a cough developing in last 6–7 months, mostly in women, non-smokers and within the sixth decade of their life. Most patients have a proven restrictive ventilation disorder.
- HRCT signs: Bilateral, symmetric reticulations with the maximal involvement in the lower pulmonary lobes. Also, traction bronchiectasis and the loss of volume of the lower pulmonary lobes, either subpleurally or diffusely can be seen. Occasionally, the subpleural areas are not affected.
- Histopathological image: A homogeneous pathology of the pulmonary interstitium, from cellular pathology to fibrosis.
- For most patients with idiopathic NSIP, a favourable course of the disease is characteristic, as there is a 5-year mortality rate of no more than 18%.

It is necessary to note that NSIP includes both the clinical diagnosis of idiopathic NSIP and the radiological and histological "pattern" of NSIP, which may be a manifestation of the lungs to a number of external or internal insults. Thus, the radiological/histological signs of NSIP can be seen in patients with HP, in pulmonary disease in SCTD, in patients with interstitial pneumonitis with autoimmune features, and in patients with familial interstitial lung disease, or in patients with a drug-induced lung disorder. Some infections can also resemble NSIP, including lung disease in patients with AIDS. In patients with a dominant fibrosing pulmonary disease, it may be difficult to distinguish NSIP from UIP or IPF, since the histological pattern of NSIP has been repeatedly seen in patients with IPF.

Note

- Since the differential diagnostics of NSIP is extensive, it is necessary to thoroughly examine these patients and consult the data obtained within the MDT.
- An important outcome is not just the diagnosis itself, but in the case of missing data, the recommendations of additional follow-up to complete the diagnosis of idiopathic NSIP.

7.2.4 Non-specific Interstitial Pneumonia—What We Should Consider in the Differential Diagnosis

1. Lung affliction in systemic connective tissue disease: Lung disorders within rheumatoid arthritis require the knowledge of the patient's history! (Fig. 7.9).
2. Drug-induced lung injury: A non-specific signs. The knowledge of the history of the use of pneumotoxic medications is required (Fig. 7.10).
3. Lung injury in non-specific intestinal inflammation: Fine fibrotic changes in the lungs bilaterally seen in a patient with Crohn's disease (Fig. 7.11).

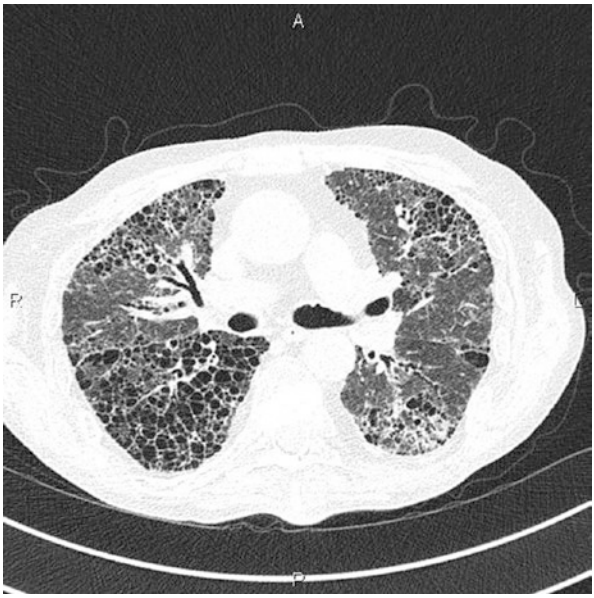


Fig. 7.9 HRCT of the lung of patient with rheumatoid arthritis: reticulations, honeycombing, small areas of GGO

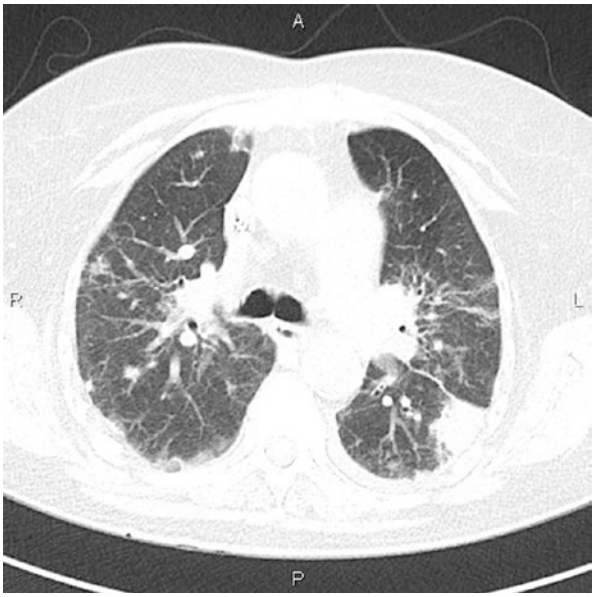


Fig. 7.10 Drug-induced lung injury: multiple nodules and consolidations in patchy distribution

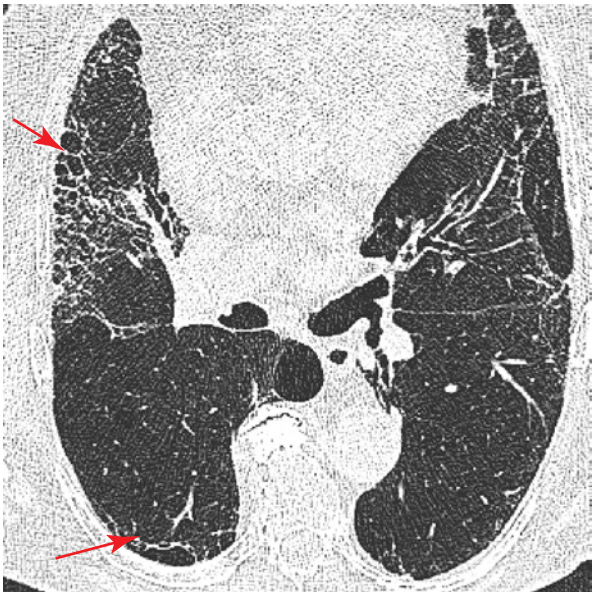


Fig. 7.11 Lung injury in non-specific intestinal inflammation: Fine fibrotic changes in the lungs bilaterally in subpleural space, areas of honeycombing

7.3 Chronic Hypersensitivity Pneumonitis

Eva Kocova and Vladimir Bartos

Female, 36 years old.
Patient examined for an irritating cough and a progressive exertional dyspnoea.

Medical History

- Without past medical history and without long-term medications.
- Family history—parents and siblings were alive, without pulmonary diseases, and her children were healthy. Had a cousin who died of lung cancer when he was 46 years old.

Occupational History and Exposure

- Without occupational exposure—teacher, working in a clean environment
- Lived in family home. In recent past, had a couple of budgerigar in an aviary at home for a couple of years
- No drug abuse
- No allergies

History of Present Compliant

- In the last year, complains of a persisting dry, irritant cough, which worsens on exertion, and has had fluctuations in body temperature. She observes dyspnoea only on exertion, which is gradually increase, although was without spontaneous attacks of dyspnoea. No other issues.

Objective Finding

- Vesicular breathing, with an occasional wheezing and crepitations. No nail clubbing present. Otherwise normal findings.

Examination

Lung Functional Tests

- VC 1.96 L/52% (ref. v), FVC 1.38 L/36% (ref. v), FEV_1 1.4 L/40%, Tiff. 68%, RV 1.89 L/132% (ref. v), TLC 3.86 L/56% (ref. v), DL_{CO} 3.98 mmol/kPa/min/53% (ref. v), K_{CO} 1.37 mmol/kPa/min/L/99% (ref. v)
- A combination of moderate to severe ventilation disorder with moderately decreased transfer factor for CO
- Six-minute walk test—walked 450 m—standard, oxygen saturation 96…84…92%, i.e. latent respiratory insufficiency

Radiology

- *Posteroanterior chest X-ray*: Raised hemidiaphragm, bilateral, bilateral nodular patterns and reticulations in the upper lobes. Furthermore, nodule in the apex of the left lung and apicalisation of the pulmonary hilar. There is no identification of vascular congestion (Fig. 7.12).

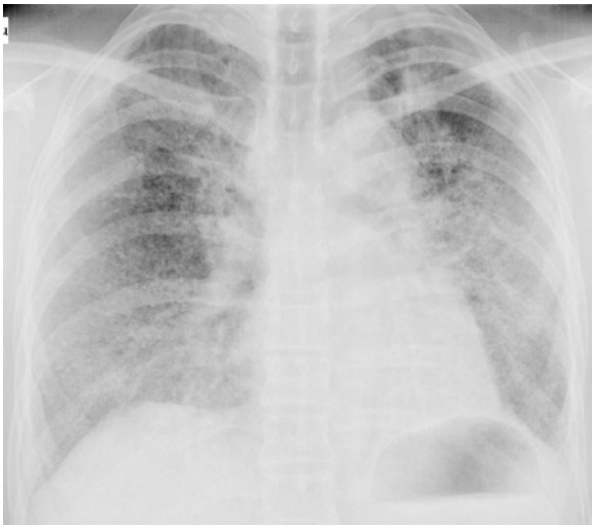


Fig. 7.12 Posteroanterior chest X-ray: bilateral coarse pulmonary markings

- *HRCT of the lungs*: Multiple centrilobular nodularities with enhancement of the central peribronchovascular interstitium. Traction bronchiectasis is noted especially in the upper pulmonary lobes, including apicalisation of the pulmonary hila and reduction of the volume of the upper pulmonary lobes (Fig. 7.13a–d).

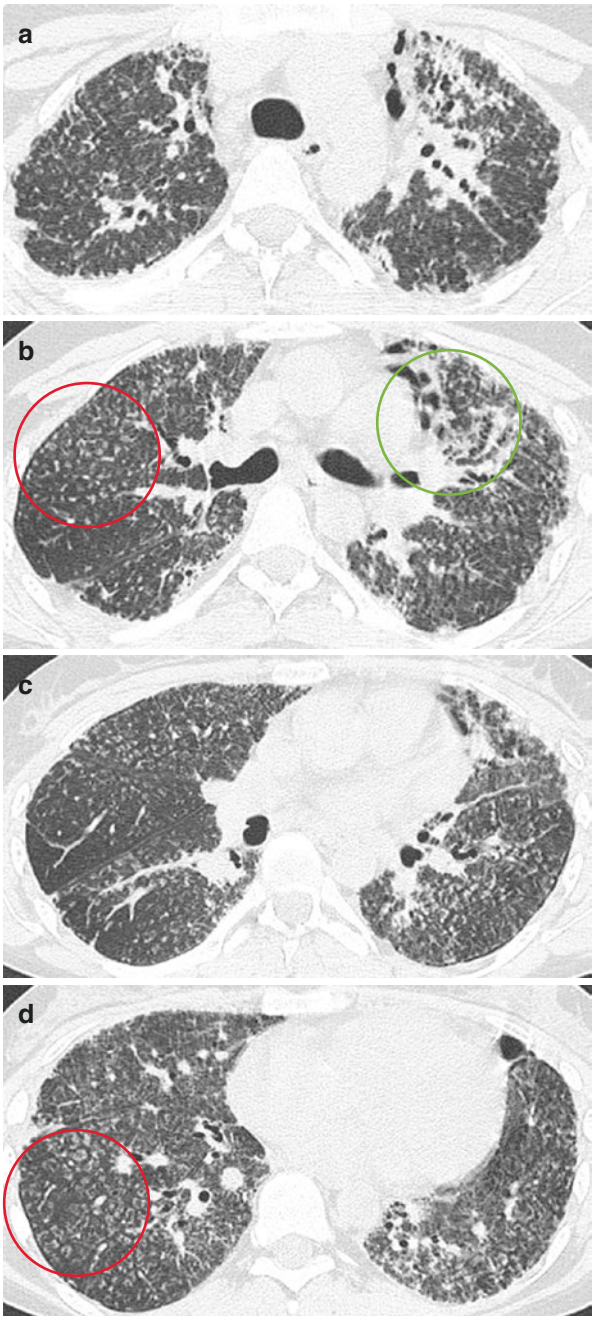


Fig. 7.13 (**a**) HRCT of the lungs: centrilobular nodules, signs of fibrosis in the upper lobes—distorsion of lung parenchyma, bronchiectasis, thickening of peribronchovascular interstitium. (**b**) HRCT of the lungs: centrilobular nodules, traction bronchiectasis. (**c**) HRCT of the lungs: centrilobular nodules, reticulations peribronchovascularly. (**d**) HRCT of the lungs: multiple centrilobular nodules

7.3.1 Multidisciplinary Team and Differential Diagnosis

The HRCT of the lung shows a fibrosing interstitial lung disease characteristic of a chronic hypersensitivity pneumonitis. Patient's symptoms lasted over 6 months and there was a history of exposure to an external antigen.

The conclusion of the MDT: Clinical and radiological signs point that this is the most likely a case of chronic hypersensitivity pneumonitis. Bronchoalveolar lavage is recommended.

Bronchoscopy and Bronchoalveolar Lavage

- Normal endobronchial finding.
- BAL: 23% alveolar macrophages, 75% lymphocytes with a pronounced predominance of CD8+ lymphocytes and 2% neutrophilic granulocytes. No malignant clonality was detected. No infection detected in cultures or by PCR methods.

Auxiliary and Laboratory Examinations

- Serological and biochemical examinations were without major deviations and were without signs of inflammation. There were no evidence of autoantibodies or immunodeficiency. HIV tests are negative. Additionally, serum angiotensin converting enzyme and soluble IL-2 receptor values were normal.

7.3.2 Conclusion

Along with HRCT imaging and the clinical presentation, the findings of lymphocytic CD8+ alveolitis and exposure to budgerigars are compatible with HP. At the request of the patient and her family, being afraid of cancer, a VATS was performed (at the time of diagnosis, cryobiopsy was not available)—histological findings were compatible with chronic active HP, partially with a honeycombing. Removal from the exposure and immunosuppressive corticosteroid therapy were recommended.

Note

- Chronic Hypersensitivity Pneumonitis is a fibrosing interstitial lung disease usually with a known allergy-inducing factor.
- Differentiation from usual interstitial pneumonia based only on HRCT images can be very difficult.

7.3.3 Chronic Hypersensitivity Pneumonitis—What We Should Consider in Differential Diagnosis

1. Fibrosing sarcoidosis: With predilection to the upper pulmonary fields, and small nodules in the perilymphatic distribution, which may create larger formations. In

the advanced stage of the disease, there is hilar apicalisation, and signs of pulmonary fibrosis (Fig. 7.14).

2. UIP: HRCT images are often very similar, however, typical UIP patterns are: changes mainly in the basal parts of the lung, rather than in the upper lobes as in HP. In both of these diagnoses, there are signs of fibrosis and traction changes. If expiratory scans are available, air trapping is seen in the case of chronic HP (Fig. 7.15).
3. Organising pneumonia: Fragmented consolidations in the periphery of the lungs, typically in the lower lobes (Fig. 7.16).
4. Eosinophilic Pulmonary Syndrome: Regions of GGO, thickening of the interlobular septa, and no nodules are present in acute phase of the disease. Centrilobular nodularities with migrating consolidations usually in subpleural zones appears in the chronic phase (Fig. 7.17).

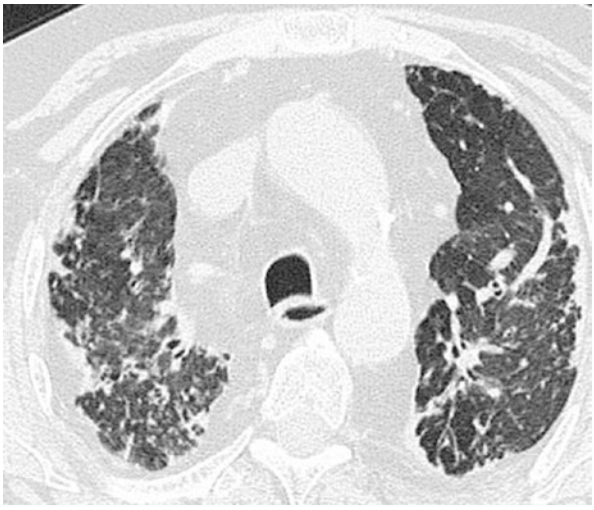


Fig. 7.14 Fibrosing sarcoidosis: Distorsion of lung parenchyma, multiple nodules in perilymphatic distribution, reticulations

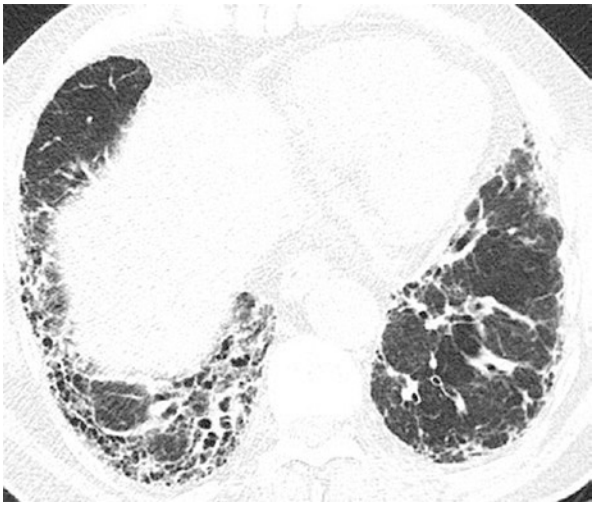


Fig. 7.15 UIP: subpleural reticulations, traction bronchiectasis, honeycombing in basal parts of the lung

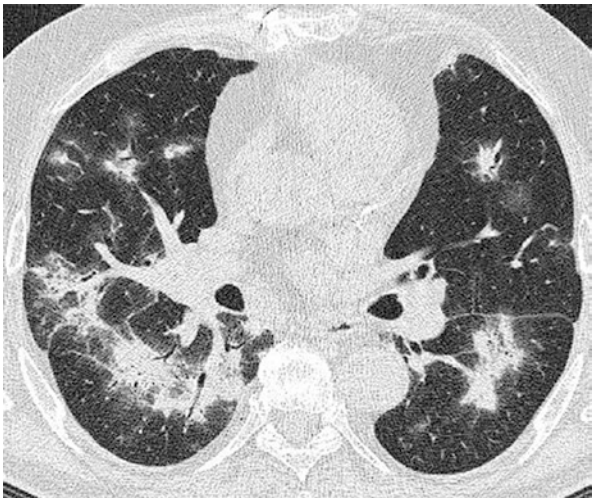


Fig. 7.16 Organising pneumonia: consolidations in the periphery of the lungs, in the lower lobes

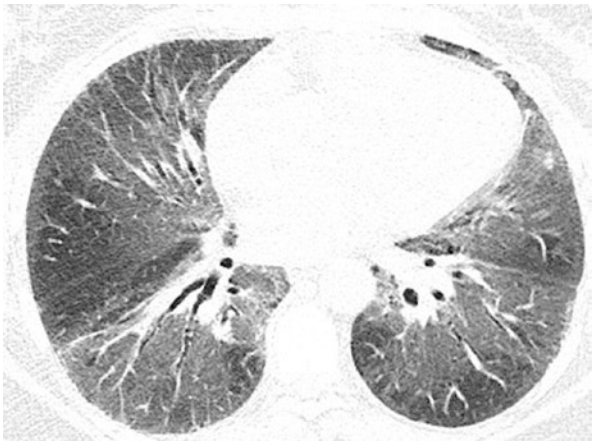


Fig. 7.17 Eosinophilic Pulmonary Syndrome: Regions of GGO and thickening of the interlobular septa

7.4 Intrapulmonary Mesothelioma

Eva Kocova and Vladimir Bartos

Male, 70 years old.
Patient admitted to complete the diagnostic process of unspecific known interstitial lung disease.

Medical History

- Ischemic heart disease, arterial hypertension, type 2 diabetes mellitus (oral anti-diabetic therapy). Otherwise insignificant, and without pneumotoxic medication

Occupational History and Exposure

- Pensioner, a former dispatcher and worked within vehicle services, with no risks for hypersensitivity pneumonitis (HP).
- Smoking history: from 15 to 35 years of age 10 cigarettes a day.

History of Present Compliant

- Progressing exertional dyspnoea in the last 6 weeks (cannot walk up more than 1 floor). Cardiological causes of the deteriorating the condition were not identified. The patient experienced weight loss, despite a normal food intake. He denies a cough, no increase body temperature, but complains of night sweats.

Objective Finding

- Vesicular breathing, bilaterally occasional rates at the base of the lungs (within about 10 cm width). Otherwise normal finding.

Examination

Lung Functional Tests

- FVC 3.28 L/73% (ref. v), FEV_1 2.8 L/83% (ref. v), Tiff. 87%, RV 2.6 L/97% (ref. v), TLC 6.1 L/81% (ref. v), RV/TLC 42%, DL_{CO} 39%, K_{CO} 65%.
- A slight decrease in resting and forced vital capacity with normal total lung capacity. There is no restrictive or obstructive ventilatory disorder, however, a severely reduced DL_{CO}. The bronchodilation test with salbutamol was negative.

Radiology

- *Posteroanterior chest X-ray*: Bilateral significant reticulations in the pulmonary parenchyma, particularly in the lower lung fields. Peripherally (more on the right) in the middle and lower lung fields, there are patches of wispy consolidations (Fig. 7.18).
- *HRCT of the lungs*: Dominant findings are bilateral peripheral GGO and reticulations. Changes clearly increase caudally, where reticulonodulations are also expressed. Rarely traction bronchiectasis can be found. There is no honeycombing (Fig. 7.19a–d).

Auxiliary and Laboratory Examinations

- Blood samples and biochemical examination were without major pathological findings, with no signs of inflammation, autoantibodies, or immunodeficiency. ENT and ophthalmological examination were physiological. Echocardiography was normal, without pulmonary hypertension, and a normal left ventricular function.

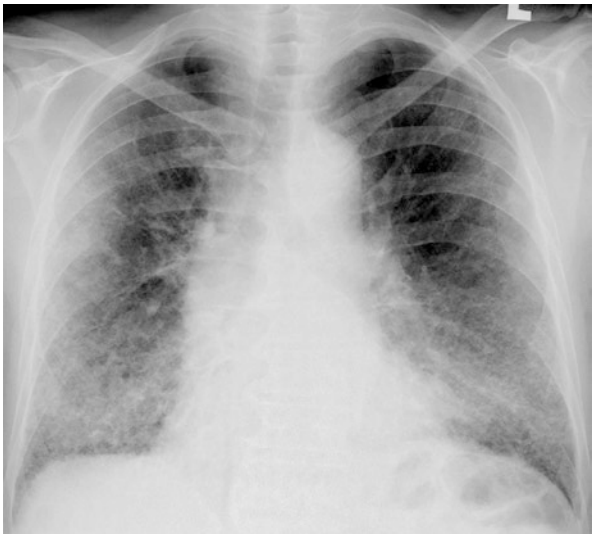


Fig. 7.18 Posteroanterior chest X-ray: Peripheral and basal reticulations

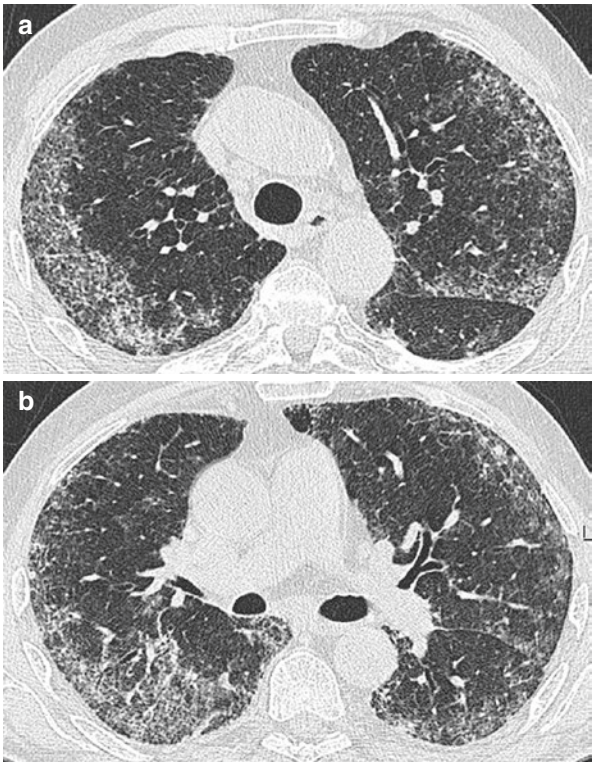
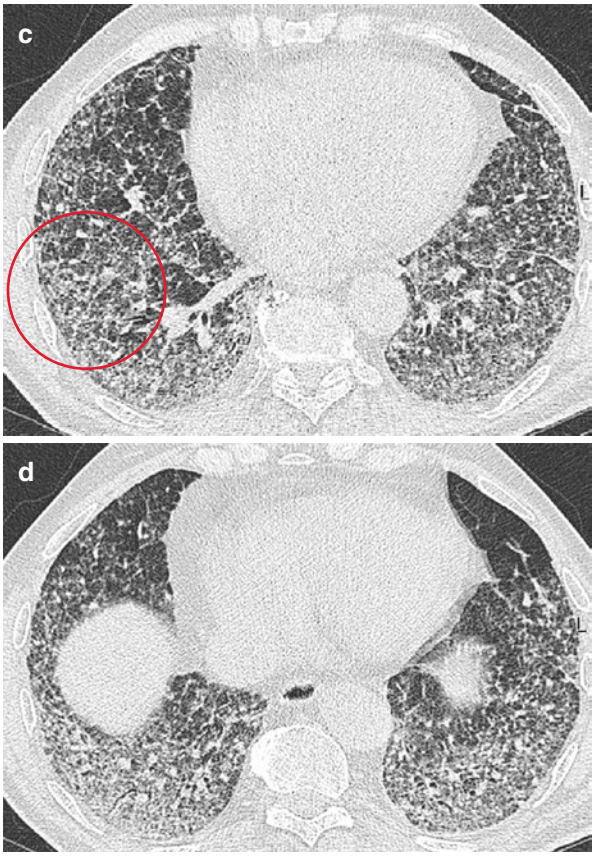


Fig. 7.19 (**a**) HRCT of the lungs: reticulations, GGO, and small nodules peripherally and subpleurally. (**b**, **c**) HRCT of the lungs: reticulations and GGO, peripherally and subpleurally. (**d**) HRCT of the lungs: reticulations and GGO, peripherally and subpleurally, mainly in dorsal parts in the lung

Fig. 7.19 (continued)



7.4.1 Multidisciplinary Team and Differential Diagnosis

Extensive ground glass opacities were the dominant morph on lung HRCT. There are few reticulations located mostly basally, and there was no sign of honeycombing. The enhancement of the peripheral interstitium was irregular, with small nodularities.

The conclusion of the MDT: Radiological signs point to a non-specific interstitial pneumonia. A bronchoalveolar lavage and rheumatological examination to rule out systemic connective tissue disease was recommended.

Bronchoscopy and Bronchoalveolar Lavage

- Normal endobronchial finding.
- BAL: cellular material, 71% alveolar macrophages, 10% lymphocytes with CD8+ lymphocytes predominance, 16% neutrophils, 2% eosinophils and 1% basophils. In addition, three more cohesive groups of cells with larger nuclei of foreign material are found.

- Conclusion: An uncommon finding, the presence of a well-differentiated adenocarcinoma cannot be ruled out. Possible SCTD was eliminated, and autoantibody and immunodeficiency tests were negative.

7.4.2 Second Multidisciplinary Team and Differential Diagnosis

Due to the presence of atypical cells in BALF, VATS was recommended for histological verification (cryobiopsy or a standard transbronchial pulmonary biopsy was not available at that time).

VATS with Left Upper Lobe Biopsy
The conclusion of the histological analysis: Undisputed findings of malignancy, morphological and immunohistochemical identification of an epithelioid variant of malignant mesothelioma, without affecting the pleura (findings of the pathologist were also confirmed in another accredited pathology clinic).

7.4.3 Conclusion

An epithelioid variant of malignant mesothelioma with intraparenchymal growth, without pleural involvement was found. The patient additionally confirmed contact with asbestosis. Chemotherapy with pemetrexed and cisplatin was initiated. Slow functional progression, and minimal bilateral progression of reticulations on plain chest X-ray was seen (Fig. 7.20). The patient died 3.5 years after the diagnosis.

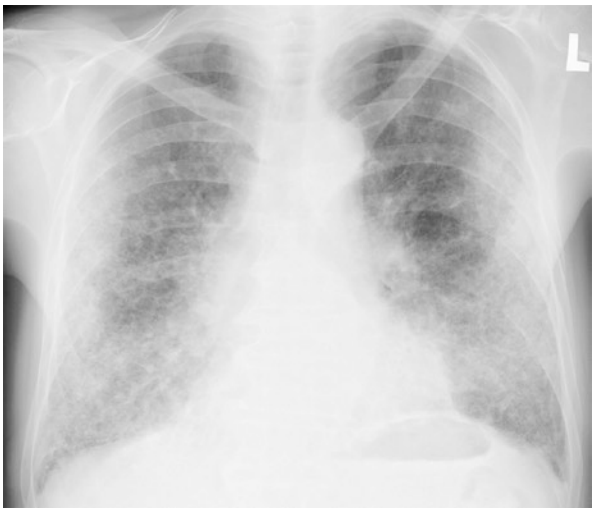


Fig. 7.20 Follow-up posteroanterior chest X-ray three years after determining the diagnosis with multiple reticulations, especially in lower lung fields

Note
Mesothelioma is a malignant disease associated with exposure to asbestos. Typically, it is located on the pleura in association with pleural plaques (Fig. 7.21). Rare cases of intrapulmonary variant of mesothelioma with affliction of the pulmonary parenchyma and no involvement of the pleura can be seen.

7.4.4 Intrapulmonary Mesothelioma—What We Should Consider in the Differential Diagnosis

1. Adenocarcinoma with lepidic growth: A diverse image on HRCT—nodules with irregular margins, sub-solid nodules, regions of consolidations of the pulmonary parenchyma with preserved air bronchogram. Regions of GGO—verification required histologically (Fig. 7.22).

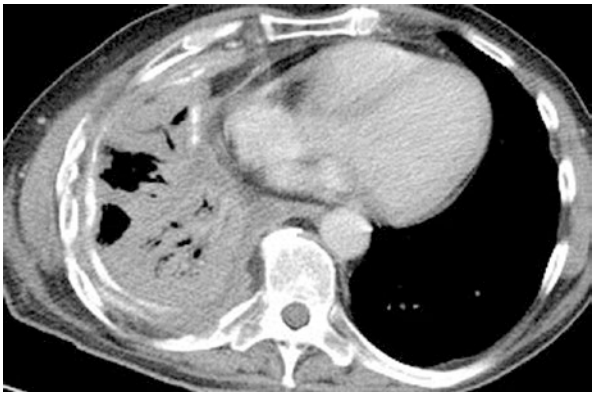


Fig. 7.21 Pleural mesothelioma with pleura thickening—typical plaques on the pleura with calcifications, fluidothorax on the right side

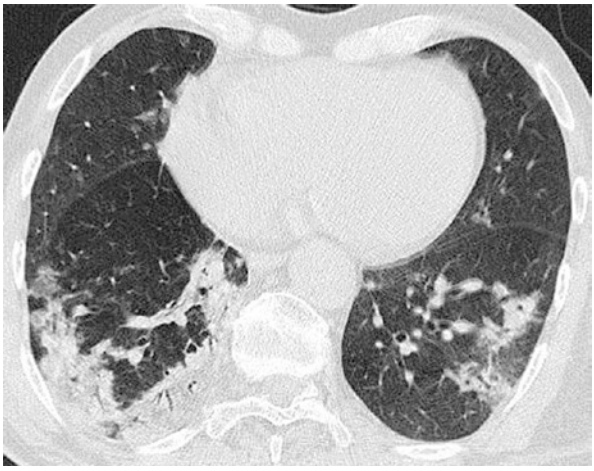


Fig. 7.22 Adenocarcinoma with lepidic growth: nodules with irregular margins, regions of consolidations with air bronchogram

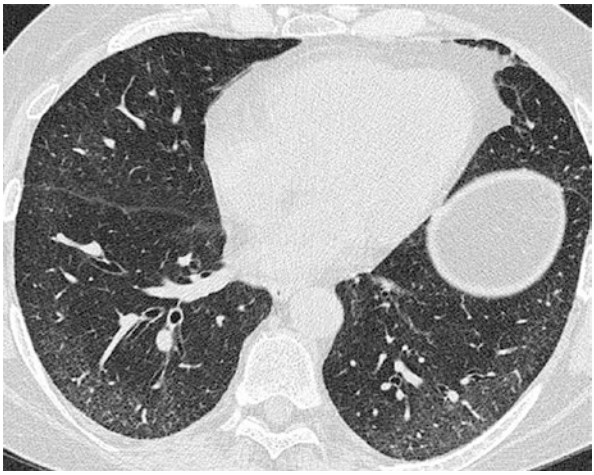


Fig. 7.23 Non-specific interstitial pneumonia (NSIP): subpleural reticulations and GGO with typical "subpleural sparing"

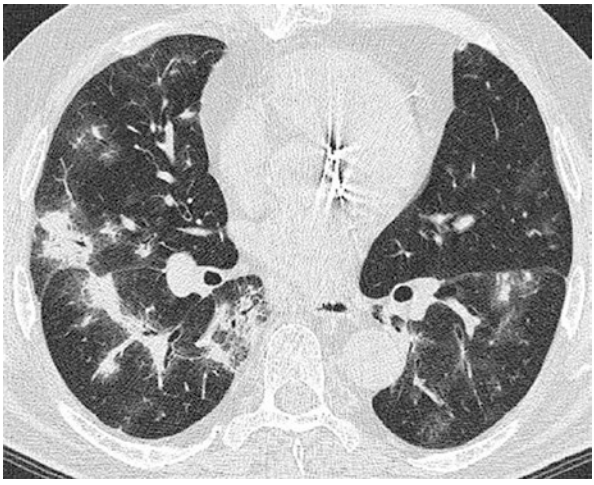


Fig. 7.24 Organising pneumonia: consolidations of the pulmonary parenchyma with a typical peripheral, subpleural and peribronchial distribution, with air bronchogram

2. Non-specific interstitial pneumonia (NSIP): HRCT of the lungs—subpleural GGO with typical "subpleural sparing" (may not be expressed!) (Fig. 7.23).
3. Organising pneumonia: HRCT of the lungs—band like consolidations of the pulmonary parenchyma with a typical peripheral, subpleural and peribronchial distribution, with air bronchogram, nodules with blurry-margined and GGO (Fig. 7.24).

7.5 Carcinomatous Lymphangiopathy I

Filip Ctvrtlik, Monika Zurkova, and Vladimira Lostakova

Male, 75 years old.

The patient was referred for mediastinal and hilar lymphadenopathy, and concurrent pulmonary disease.

With recurrent long-term dyspnoea and cough, and after repeated examinations, the patient's case was closed as suspected sarcoidosis by the local physician.

Medical History

- Type 2 diabetes mellitus (on oral anti-diabetic therapy), and arterial hypertension

Occupational History and Exposure

- Pensioner, former forest worker
- Married, has four children, lives in a family home, no pets/animals
- Smoking history: Ex-smoker, quit smoking at 40 years of age, previously smoked 40 cigarettes a day for 12 years

History of Present Compliant

- Gradual progressive dyspnoea at minimal exertion and a cough with the production of white sputum in the last 1½ month weight loss of 8 kg in 4 months, loss of appetite, and the occasional abdominal pain.

Objective finding

- Resonant lung percussion, vesicular breathing and bilateral crepitations

Examination

Lung Functional Tests

- VC 2.20 L/53% (ref. v), FEV_1 1.77 L/58% (ref. v), TI% VC_{max} 81% (ref. v), MEF25 45% (ref. v), TLC 60% (ref. v), RV 77% (ref. v), R_{tot} 0.42
- Moderate restrictive ventilatory disorder, low RV, increased airway resistance
- DL_{CO}sb: DL_{CO} 39% (ref. v), K_{CO} 78% (ref. v)
- Severe reduction of transfer factor with a mild reduction of transfer coefficient

Auxiliary and Laboratory Examinations

- Elevation of prostate specific antigen (PSA) to 867.
- Signs of respiratory insufficiency on arterial blood gas: pCO_2: 4.10, pO_2: 6.85 and saturation 85.6% without support.

Radiology

- *Posteroanterior chest X-ray*: Multiple, almost diffuse reticulonodulations in both lobes. Pulmonary vascular markings are unassessable. The diaphragm is blurred and costophrenic angles are blunt. Heart shadow size is normal. A fracture is noted on the left IX rib (Fig. 7.25).

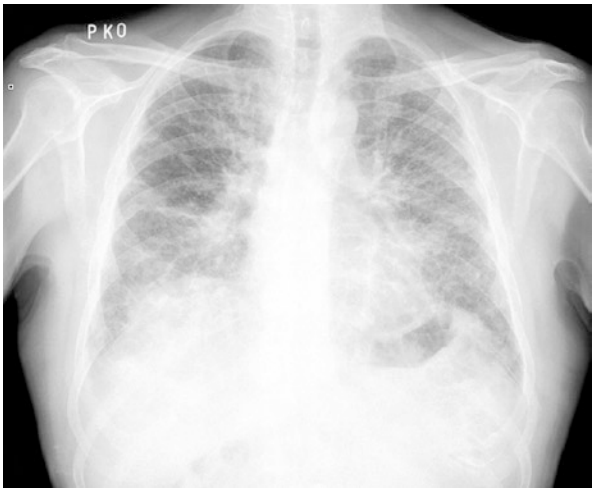


Fig. 7.25 Posteroanterior chest X-ray: fracture of the IX rib on the left in the axillary line with osteolytic clarification

- *CT of lungs and abdomen*: Almost symmetric thickening of the interlobular septa, prevalent in the cranial parts of the lungs, mostly on the left, is dominant. Barely noticeable are small nodules, mostly on the interlobar fissure. Otherwise, normal pulmonary architecture is apparent. There is asymmetrically enlargement of lymph nodes (predominantly paratracheal and subcarinal) in the mediastinum. A combination of osteoplastic and osteolytic bone areas. CT of abdomen with contrast—the prostate is enlarged and merges with the ventral wall of the rectum (Figs. 7.26a–d and 7.27a–c).

7.5.1 Multidisciplinary Team and Differential Diagnosis

The pathological fracture of the left IX rib is clearly visible on a simple chest X-ray (patient repeatedly denies trauma), and is suspicious of a malignancy. Chest and abdominal CT with intravenous contrast medium was performed. The distribution of the findings and the multiple skeletal lesions mean sarcoidosis is unlikely. The combination of osteoblastic and osteolytic lesions leads to the possibility of prostatic carcinoma.

Bronchoscopy and Bronchoalveolar Lavage

- Bronchoscopy + BAL: Patient refused.

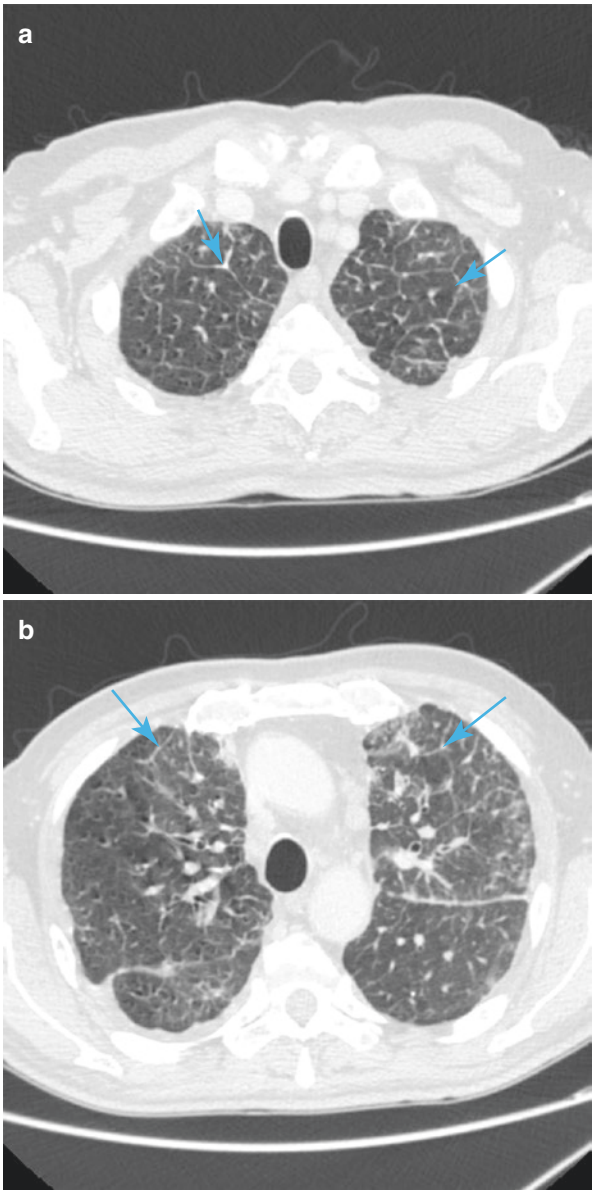
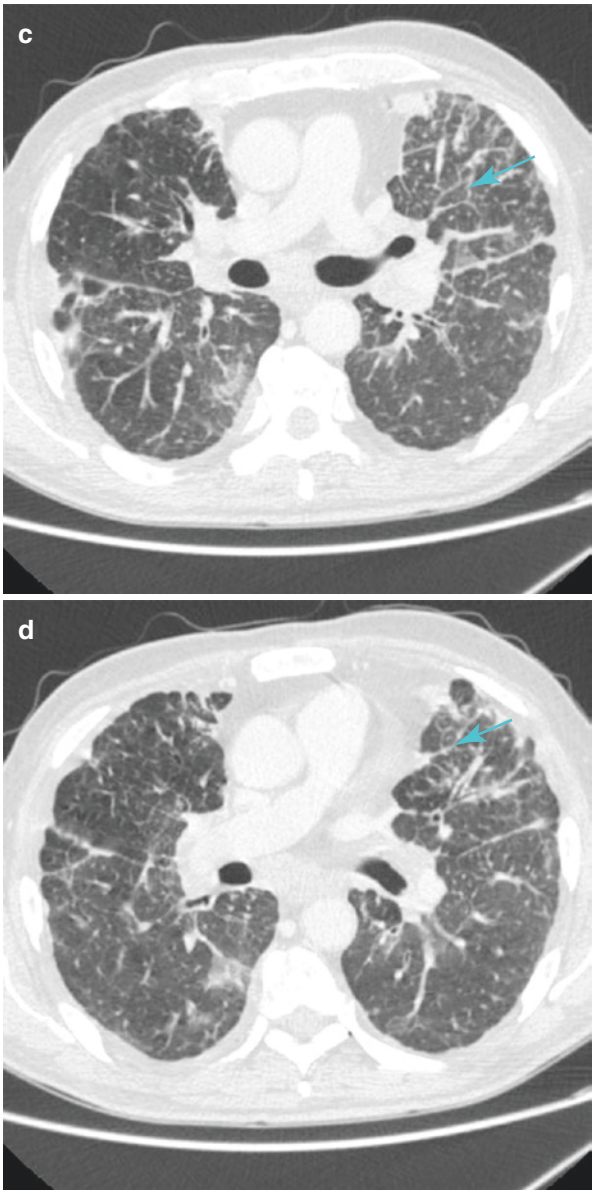


Fig. 7.26 (**a**) CT of the lungs with contrast medium i.v.: symmetric thickening of the interlobular septa. (**b**) CT of the lungs with contrast medium i.v.: thickening of the interlobular septa. (**c**) CT of the lungs with contrast medium i.v.: thickening of the interlobular septa with small nodules. (**d**) CT of the lungs with contrast i.v.: thickening of the interlobular septa with small nodules

Fig. 7.26 (continued)



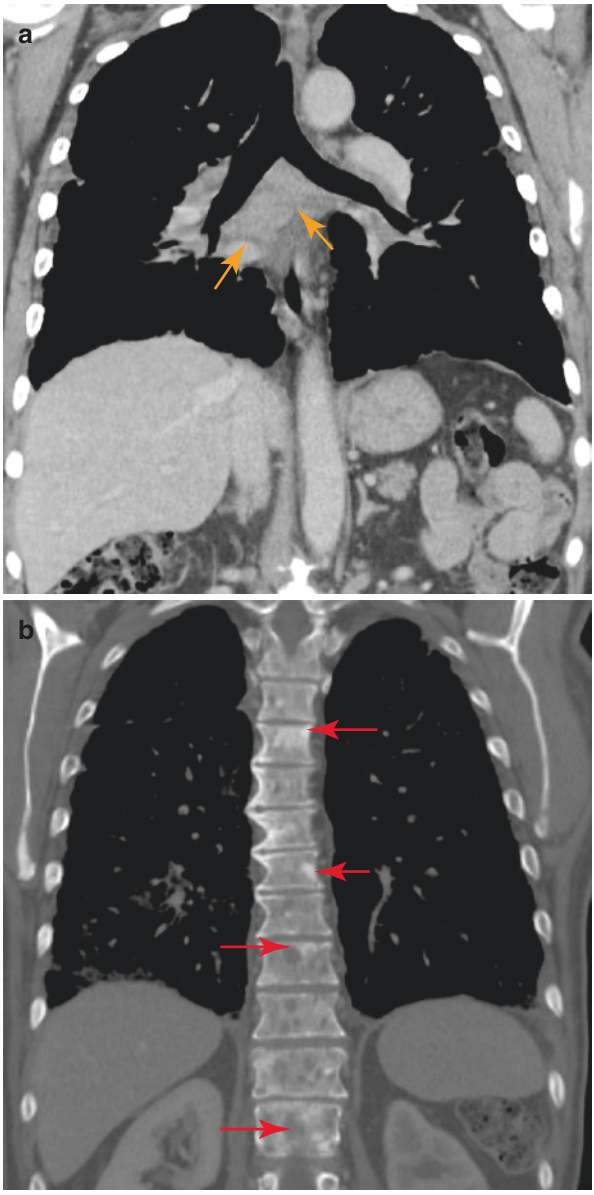
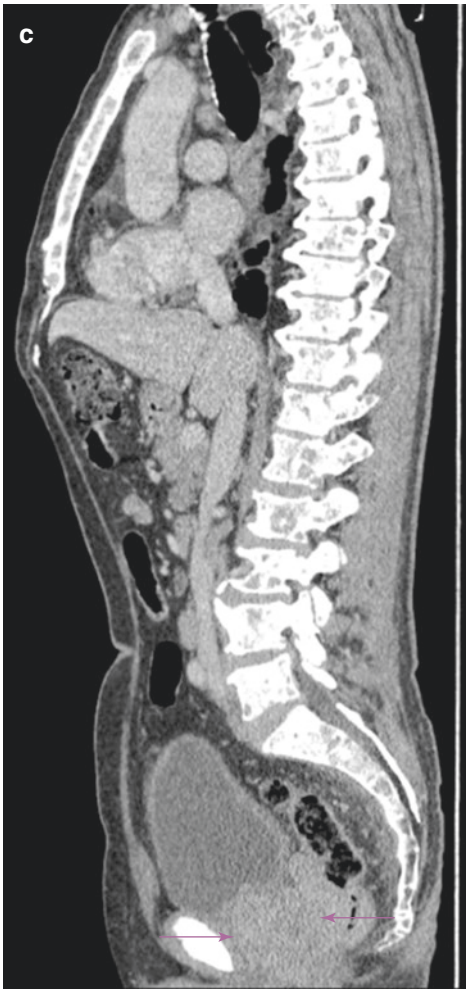


Fig. 7.27 (**a**) CT of the lungs with contrast medium i.v. (coronal scan, mediastinal window): asymmetrically enlarged mediastinal lymph nodes. (**b**) CT of the lungs with contrast medium i.v. (coronal scan, bone window): a combination of osteoplastic and osteolytic lesions. (**c**) CT of the chest and abdomen with contrast medium i.v. (sagittal scan, mediastinal window): noticeably enlarged prostate with coalescence to ventral wall of the rectum. Heterogeneous bone structure

Fig. 7.27 (continued)



7.5.2 Conclusion

Findings on the chest CT, abdominal CT, and the raised PSA lead to suspicion that the pathology of the lung interstitium is metastatic prostate tumour. A urological examination was completed with a biopsy of prostate. Prostate adenocarcinoma was confirmed. The patient refused bronchoscopy. Treatment options were discussed with a urologist and the patient agreed on surgical castration. Long-term home oxygen therapy (LTOT) was indicated for respiratory insufficiency. The patient died within few months after the diagnosis.

Note

- Carcinomatous lymphangiopathy occurs mainly in the following tumours: lung, breast, prostate, pancreas, stomach, colon, thyroid gland and uterine neck.
- Carcinomatous lymphangiopathy usually affect lungs bilaterally but may be unilateral (e.g. adjacent to a lung carcinoma).
- If carcinomatous lymphangiopathy is present in both lungs and with the presence of nodules, it may be misdiagnosis as sarcoidosis. Malignancy in medical history or pathological findings in other organs are a key for a correct diagnosis.
- In this case, the pathological rib fracture on chest X-ray and bone metastases on the CT led to the diagnosis.

7.5.3 Carcinomatous Lymphangiopathy—What We Should Consider in the Differential Diagnosis

1. Pulmonary oedema: Oedema secondary to cardiac aetiology is indicated by cardiomegaly and the accompanying pleural effusion. In the majority of cases, the fluidothorax is bilateral. In pulmonary oedema, thickened interlobular septa and sometimes GGO is seen on HRCT. Clinically, pulmonary oedema is in contrast to carcinomatous lymphangiopathy, accompanied by acute symptomatology (Fig. 7.28).

   (Note: It is necessary to realise that interstitial pulmonary oedema may be not only of cardiac but also non-cardiac aetiology (e.g. ARDS). This means that the cardiological findings (HRCT and ECHO examinations) may be normal in non-cardiac pulmonary oedema.

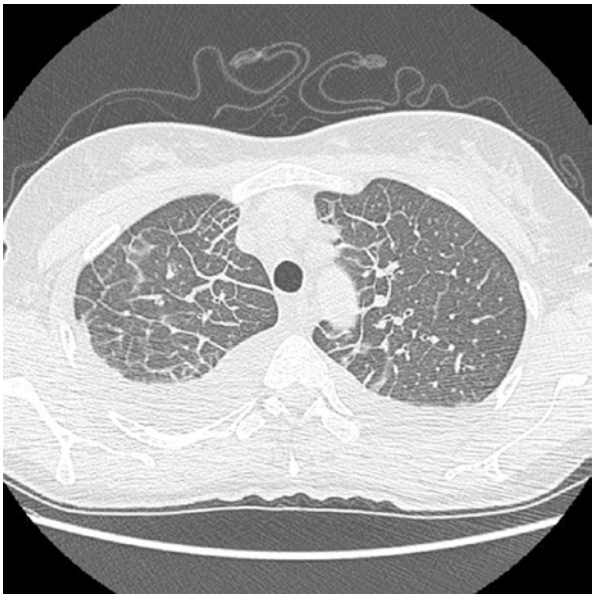


Fig. 7.28 Cardiac oedema with thickening of interlobular septa, fluidothorax on the right side

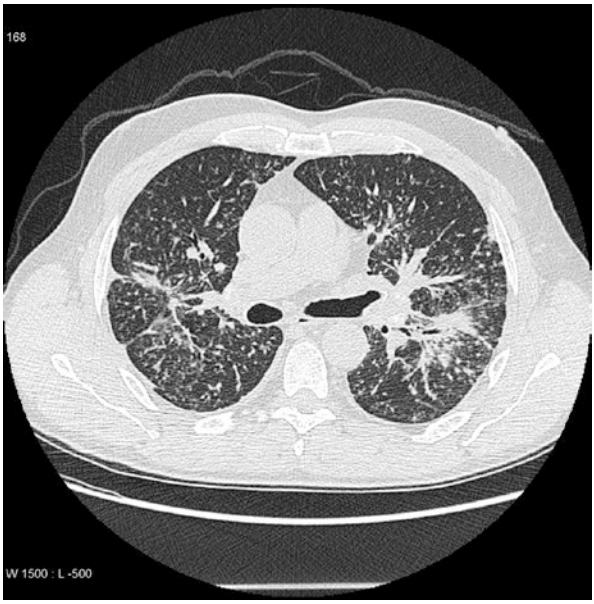


Fig. 7.29 Sarcoidosis: bilateral nodules in perilymphatic distribution

2. Sarcoidosis: The lungs tend to be affected asymmetrically in sarcoidosis and the dominant patterns are nodules (in a perilymphatic distribution). On the other hand, bilateral thickening of interlobular septa and fluidothorax are also atypical for sarcoidosis. It is usually seen in younger patients with chronic symptoms (Fig. 7.29).

7.6 Pulmonary Disease in Systemic Scleroderma

Eva Kocova and Vladimir Bartos

Female, 76 years old.
Referred from the rheumatological clinic for dyspnoea, with known systemic connective tissue disease—scleroderma.

Medical History

- Systemic scleroderma affecting the skin, oesophagus, and lungs.
- Positive for SCL70, anti-Ro and anti-La autoantibodies for 10 years.
- Raynaud's phenomenon of the upper and lower extremities.
- Secondary Sjögren's syndrome—monitored by a rheumatologist, and treated with long-term oral corticosteroids and combined immunosuppressive therapy; also, history of intermittent treatment of corticosteroids and cyclophosphamide.

Occupational History and Exposure

- Retired, a former clerk, worked in a clean, non-risk environment
- Lives in a flat without animals
- Smoking history: nil

History of Present Compliant

- The patient was referred by a rheumatologist to the ILD clinic, to be reviewed for progressive exertional dyspnoea and a dry cough (previously treated with inhaled corticosteroids—budesonide from a respiratory physician).

Objective Finding

- Vesicular breathing and bilateral crepitations between the scapulae. Typical signs of scleroderma—microstoma, perioral radial furrowing, macerated hardened skin especially on the acral parts of the limbs, and Raynaud's phenomenon of the upper and lower limbs when exposed to cold.

Examination

Lung Functional Tests

- FVC 1.42 L/67% (ref. v), FEV_1 1.28 L/74% (ref. v), Tiff. 81%, TLC 3.42 L/71% (ref. v), RV 1.71 L/82% (ref. v), DL_{CO} 47% (ref. v).
- Mild restrictive ventilatory defect, no obstruction. Moderate limitation of transfer factor for CO.

Radiology

- *HRCT of the lungs*: Bilateral reticulations and signs of fibrosis, with reduced volume of the lower lobes and traction bronchiectasis. Basal ground glass opacities, predominantly on the right. Oesophageal dilation is also noted (Fig. 7.30a–d).

7.6.1 Multidisciplinary Team and Differential Diagnosis

HRCT of the lungs showed signs of fibrosis with traction bronchiectasis, GGO basally in a patient with the history of SCTD.

The conclusion of the MDT: Clinically and radiologically, we see interstitial lung disease with systemic connective tissue disease. BAL is recommended to determine disease activity and possible opportunistic infections. Echocardiography is recommended to detect possible pulmonary hypertension.

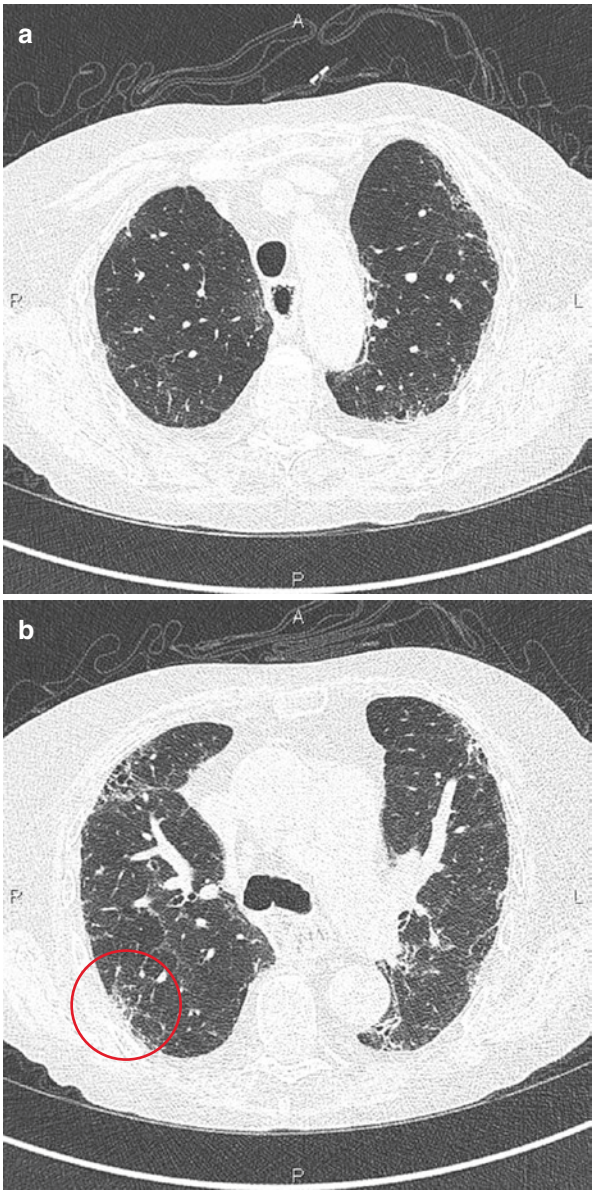
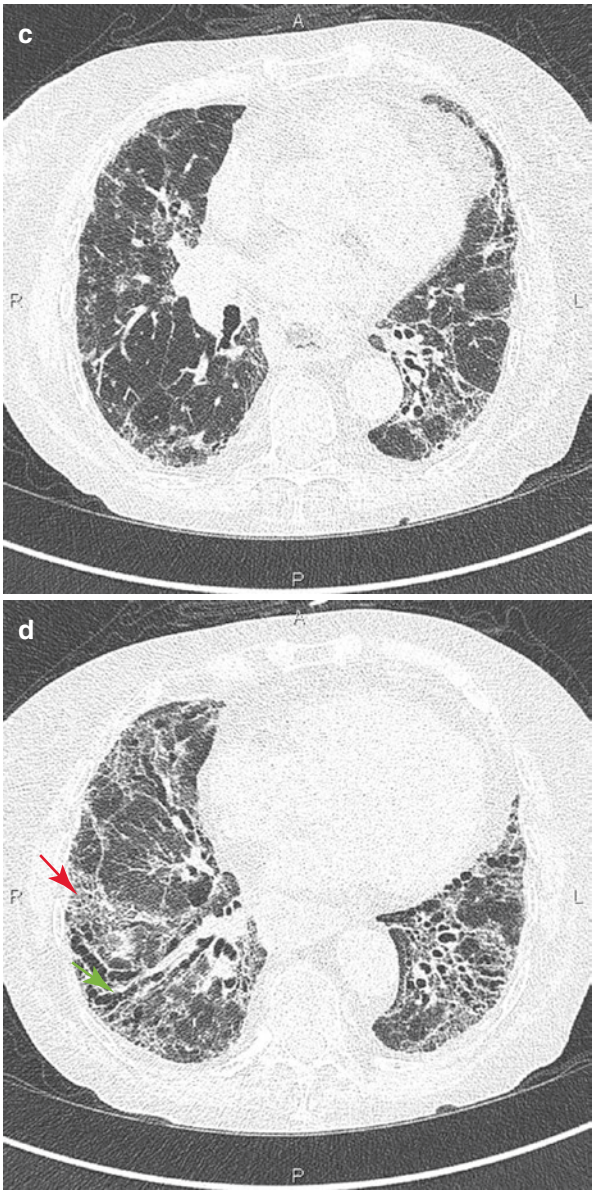


Fig. 7.30 (**a**) HRCT of the lungs: fine reticulations subpleurally. (**b**) HRCT of the lungs: reticulations especially subpleurally. (**c**) HRCT of the lungs: traction bronchiectasis, reticulations. (**d**) HRCT of the lungs: traction bronchiectasis bilateral lower lobe volume reduction with a shift of the interlobar fissure—signs of fibrosis

Fig. 7.30 (continued)



Bronchoalveolar Lavage

- 93% alveolar macrophages, 7% lymphocytes, and less than 1% neutrophils. Negative staining of mycobacteria, mycotic or tumorous processes. Culture and PCR are without evidence of infection.

Echocardiography

- Normal findings, with no evidence of pulmonary hypertension.

7.6.2 Conclusion

The lung interstitial disease is representative of UIP in scleroderma. An infection cause for worsening dyspnoea was not identified by BAL. Echocardiography was normal, without explanation for worsening of symptoms. The MDT recommended anti-reflux (as microaspiration could not be excluded), pulmonary rehabilitation and nutritional support. Immunosuppressive therapy was continued but the doses and choice of therapy was very limited due to poor tolerance by the patient.

Note
Pulmonary disease associated with scleroderma usually shows UIP-like patterns. CT shows predominant dorsobasal bilateral reticulations, bronchiectasis, and honeycombing, or can present as NSIP with prevailing GGO, and reticulations. Typically, a dilated oesophagus is associated with frequent complications such as aspiration pneumonia. Pleural effusions are not typical for scleroderma, but are often associated with other systemic connective tissue diseases.

7.6.3 Pulmonary Disease in Systemic Scleroderma—What We Should Consider in Differential Diagnosis

1. Usual interstitial pneumonia, clinically idiopathic pulmonary fibrosis: Radiologically indistinguishable if the pattern of pulmonary affliction in scleroderma UIP-like. However, dilated oesophagus is not seen in idiopathic pulmonary fibrosis) (Fig. 7.31).
2. Drug-induced interstitial lung disease: The HRCT may have variable signs of damage: consolidations, GGO, and NSIP-like patterns. Usually with a history of use of possible pneumotoxic medications (Fig. 7.32).
3. Asbestosis: Pleural plaques—calcified and non-calcified, combined with a history of asbestos exposure (Fig. 7.33).
4. Chronic hypersensitivity pneumonitis: Suspected or proven exposure to organic antigens, fibrosis on CT, air trapping and centrilobular sub-solid nodules (Fig. 7.34).

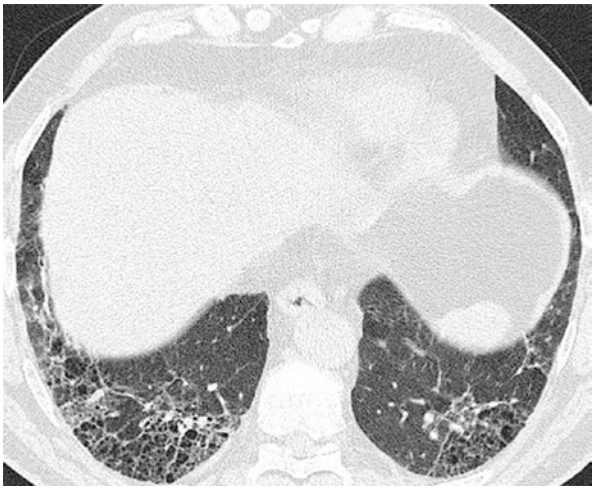


Fig. 7.31 HRCT of the lung: UIP with signs of reticulations, honeycombing and traction bronchiectasis

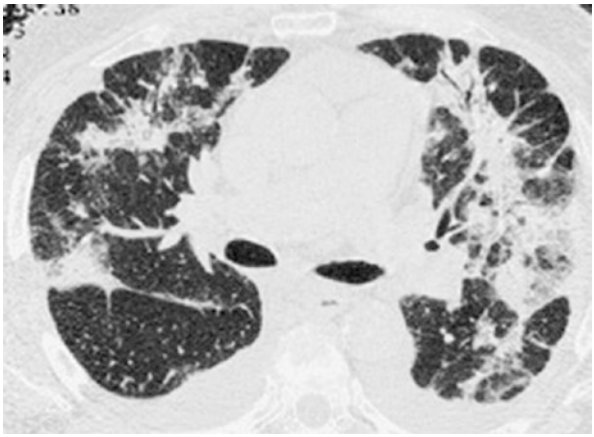


Fig. 7.32 Drug-induced interstitial lung disease: The HRCT with patchy consolidations

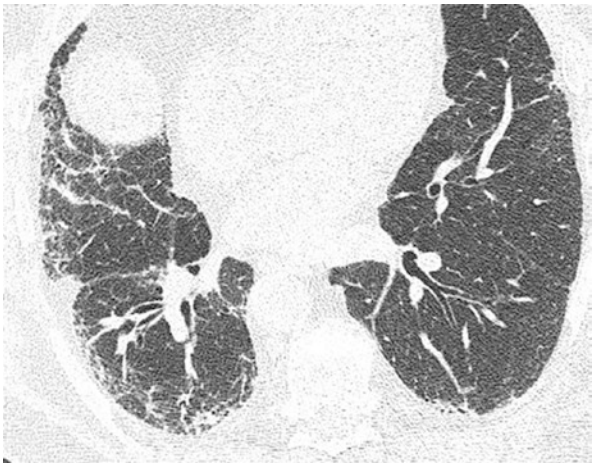


Fig. 7.33 Asbestosis: subpleural reticulations, pleural plaques

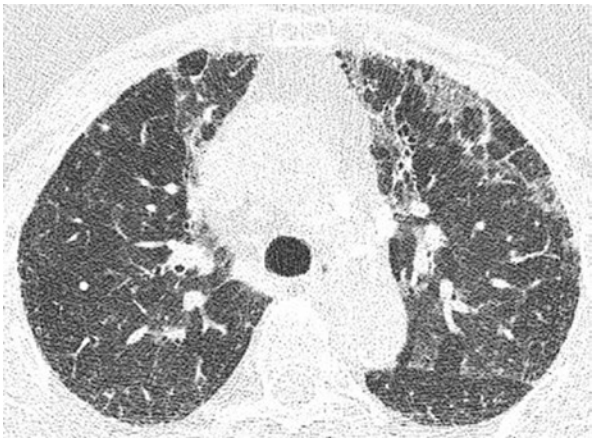


Fig. 7.34 Chronic hypersensitivity pneumonitis: GGO, reticulations, peribronchial thickening

7.7 Familial Interstitial Lung Fibrosis

Eva Kocova and Vladimir Bartos

Female, 33 years.

A persistent cough.

Medical History

- Insignificant—until now healthy, without long-term medications.

Family History

- The patient's father died 1 year ago from an unidentified pulmonary fibrosis disorder, and her mother was treated for fibrosing interstitial pulmonary disease.

Occupational History and Exposure

- Non-risk exposure, office worker within a clean environment
- Lives with family in a home, without animals, no mould, no whirlpool use, no hobbies or surrounding risks for HP
- Smoking and alcohol history: long-term non-smoker, abstinent

History of Present Complaint

- Over the last year, the patient had repeated "respiratory infections" (always without fever, laboratory examinations were not performed). A chest X-ray was performed for suspected pneumonia, which revealed areas of reticulation. Due

to the persistent pathological sounds and an unresolved cough despite antibiotic therapy, HRCT of the lungs was performed. She was referred to pulmonologist for further examinations at a specialised Department of Respiratory Medicine, where at the same time, the patient was found to be in her 6 week of pregnancy.

Objective Finding

- Vesicular breathing, basal crepitations/rales. Otherwise normal.

Examination

Lung Functional Tests
- VC 3.05 L/90% (ref. v), FVC 2.67 L/75% (ref. v), FEV_1 2.63 L/85% (ref. v), Tiff. 97%, TLC 5.53 L/107% (ref. v), RV 2.48 L/128% (ref. v), RV/TLC 51, DL_{CO} 6.11/70% (ref. v), K_{CO} 1.2/78% (ref. v)
- A mild reduction in forced vital capacity, a normal resting vital capacity, with no restrictive or obstructive ventilatory disorder. There is a mild limitation of transfer factor for CO.

Bronchoscopy and Bronchoalveolar Lavage
- Normal endobronchial findings.
- BAL: 94% alveolar macrophages, 2% lymphocytes, slight CD4+ lymphocyte predominance over CD8+ lymphocytes, 3% neutrophils and 1% neutrophils. Malignant structures or infection were not found.

Radiology
- *HRCT of the lungs*: Bilateral subpleural reticulations expressed in a craniocaudal gradient, with some ground glass opacities. Rare dorsobasal traction bronchiectasis was present. Honeycombing, mediastinal or hilar lymphadenopathy were not found (Fig. 7.35a–c).

7.7.1 Initial Multidisciplinary Team and Differential Diagnosis

The HRCT signs represent fibrosing ILD of a possible UIP character—reticulations with maximum dorsobasal and bilateral predilection—changes suggestive of UIP. The clinical presentation was a dry cough without any other problems and a mild restrictive pulmonary defect. This very young pregnant patient, desiring to continue her pregnancy, rejects any potential high-risk treatment towards the foetus.

The conclusion of the MDT: The radiological image corresponds to possible UIP. In light of the pregnancy, changes on regime were recommended. SCTDs need to be ruled out as soon as possible.

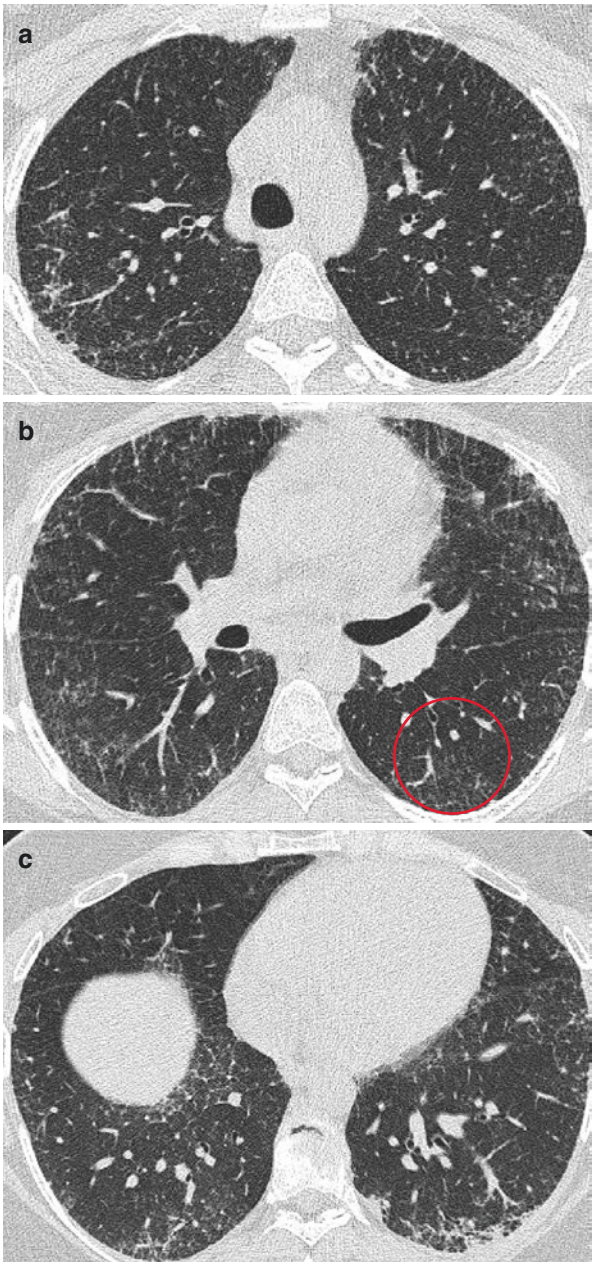


Fig. 7.35 (**a**–**c**) HRCT of the lungs: subpleural reticulations

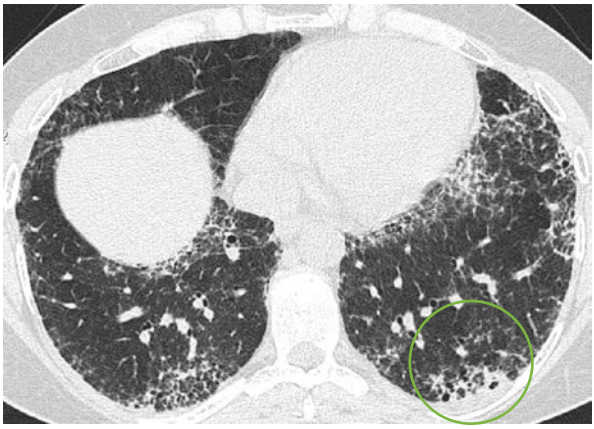


Fig. 7.36 Follow-up HRCT of the lungs: reticulations and traction bronchiectasis

Auxiliary Examination and Follow-up

- SCTD was excluded by the rheumatologist, and no autoantibodies were detected. An immunologist excluded allergies and immunodeficiency, and there was no evidence of antibodies indicating possible HP.
- The pregnancy and childbirth remained without complications (the patient refused immunosuppressive therapy during pregnancy). The patient attended regular check-ups where decrease in transfer factor for CO and a slow decline in FVC were seen. After childbirth, a reassessment with HRCT was performed with findings of advanced reticulations in the lungs (Fig. 7.36).

7.7.2 Second Multidisciplinary Team and Differential Diagnosis

A young patient with a fibrosing interstitial lung disease in progression over the last 11 months. A slow decline of FVC and DL_{CO} was seen. VATS with histological verification was recommended.

VATS with Histological Sampling

- A sign of an ILD with age-related changes with varying distribution, fibroblasts, and a minimal inflammatory response—these are signs of usual interstitial pneumonia (UIP). With respect to the age of the patient, the findings were also consulted at Mayo Clinic, USA, with the same conclusion.

7.7.3 Conclusion

The pathological-radiological findings are compatible with UIP, without identifiable secondary cause. The conclusion of the findings was familial pulmonary

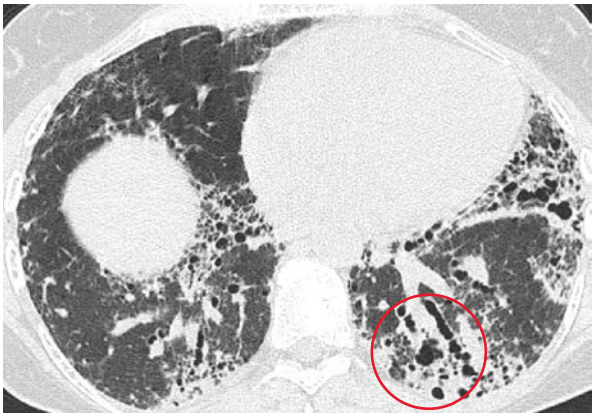


Fig. 7.37 Follow-up HRCT: progression of fibrotic changes with voluminous bronchiectasis

fibrosis with histological and HRCT verification of UIP. The case was repeatedly consulted with rheumatologist, and there was no development of systemic connective tissue disease. The disease progressed despite combined immunosuppression. High-dose pulse corticosteroids therapy followed (five cycles of 1 g of methylprednisolone i.v.) but was without effect. Despite treatment, 5 years from diagnosis the gradual disease progression was followed by development of respiratory failure, requiring the need for long-term home oxygen therapy. A HRCT scan performed 5 years after the diagnosis revealed progressive fibrotic changes with widespread bronchiectasis (Fig. 7.37). The patient underwent a successful transplant of both lungs, but unfortunately died of multi-organ failure due to a resistant cytomegalovirus infection 1 year later.

7.8 Mother of the Patient Also in Care—66 Years Old

Medical History

- In now

Occupational History

- Pensioner, formerly working in a dusty environment—electric motor production line
- Smoking history—from 17 to 40 years of age smoked 5 cigarettes a day

History of Present Complaint

- Observing exertional dyspnoea and pain between the scapulae in the last year. Increased dyspnoea and fever in the last week. The patient was admitted for bilateral pneumonia.

Objective Finding

- Vesicular breathing, basal crepitations, subfebrile, and respiratory insufficiency.

Examination

Lung Functional Tests

- FVC 1.73 L/67% (ref. v), FEV_1 1.64 L/76% (ref. v), Tiff. 92%, TLC 3.20 L/64% (ref. v), RV 1.42 L/72% (ref. v), DL_{CO} 2.28/31% (ref. v), K_{CO} 0.84/57% (ref. v)
- Mild restrictive ventilatory disorder without obstruction, severely limited pulmonary diffusion for CO

Radiology

- *HRCT of the lungs*: Extensive regions of GGO, especially basally, with regions of preserved pulmonary tissue. Signs of pulmonary fibrosis with extensive traction bronchiectasis, and without apparent honeycombing (Fig. 7.38a–d).

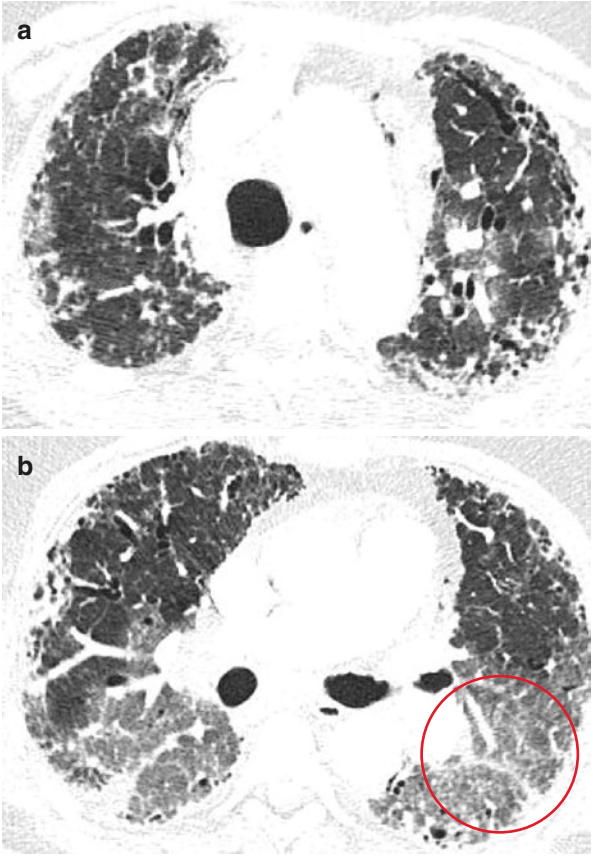
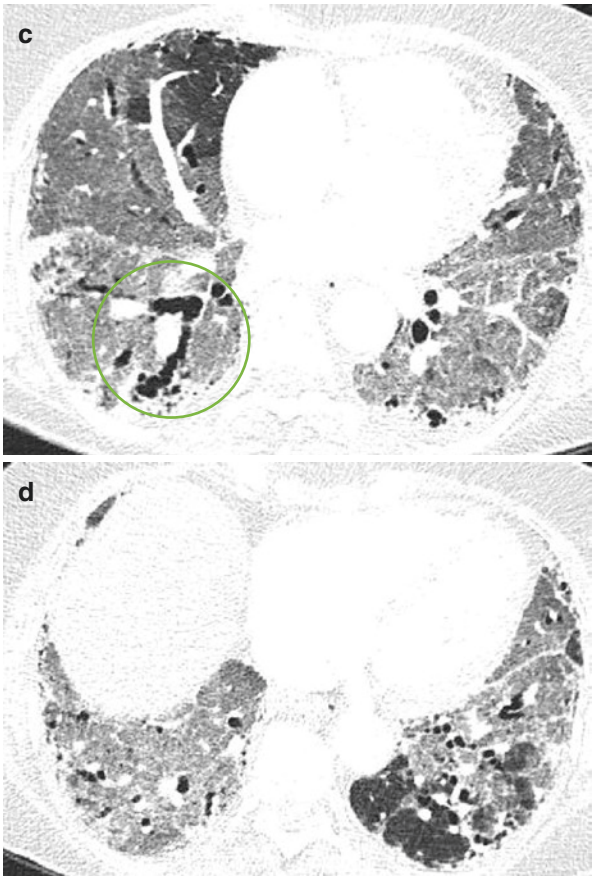


Fig. 7.38 (**a–d**) HRCT of the lungs: extensive GGO and traction bronchiectasis

Fig. 7.38 (continued)



7.8.1 Multidisciplinary Team and Differential Diagnosis

A fibrosing interstitial lung disease with extensive GGO, with the probable involvement of a bilateral infection. The patient is febrile. Her daughter was treated for interstitial pulmonary fibrosis of UIP pattern.

7.8.2 Conclusion

Familial pulmonary fibrosis, probably in coincidence with an infectious aetiology. BAL is recommended. The exclusion of SCTD is required.

Bronchoalveolar Lavage

- BAL: 31% of alveolar macrophages, 7% of lymphocytes, 11% of eosinophils, 51% of neutrophils. No haemorrhage. The infectious agents could not be detected by PCR.

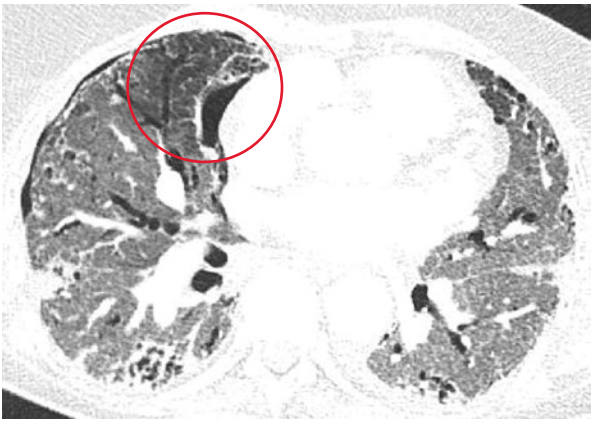


Fig. 7.39 HRCT follow-up after 2 months: progression of GGO, new pneumothorax on the right

Despite established antibiotic and empiric antimycotic therapy, the patient's condition rapidly progressed. Corticosteroid therapy was initiated. The patient required non-invasive pulmonary ventilation due to the progression of type II respiratory insufficiency. A follow-up HRCT revealed progressive findings of GGO and identified a spontaneous pneumothorax on the right side (Fig. 7.39). The BAL was without evidence of infection, and corticosteroid pulse therapy was without effect. Despite the combined anti-infective and immunosuppressive therapy, the disease progressed. The patient refused invasive pulmonary ventilation, and due to the unfavourable prognosis, the patient died soon after.

Note
Familial interstitial lung diseases may have different HRCT presentations and clinical course. Individual family members also often have different HRCT images and clinical course.

7.9 Idiopathic Pulmonary Fibrosis I

Martina Sterclova, Jana Votrubova, and Eva Kocova

Male, 62 years old.

The patient presents with exertional dyspnoea that he has been observing for several years, and over time his symptoms are progressively worsening.

Medical History

- No significant medical treatments

Occupational History and Exposure

- Works as a technician in the food industry, operating for a maximum of 1 h a day
- Lives with family in a flat that has a dry environment, keeps a dog and a cat
- Smoking history: lifelong non-smoker

History of Present Complaint

The patient was treated within a respiratory department for the first time 3 years ago, for the suspicion of asthma. The patient was found not to have asthma, and furthermore the patient's symptoms spontaneously disappeared. However, along with other examinations, the patient underwent a chest HRCT, and changes corresponding to interstitial lung disease were identified. He was further assessed by a pulmonologist. Three years later, he attended an appointment and complained of exertional dyspnoea. He does not have a cough and does not have a temperature.

Objective Finding

- Vesicular breathing, basal crepitations, no nail clubbing.

Examination

Lung Functional Test

- FVC 3.96 L/101% (ref. v), VC_{max} 3.98 L/98% (ref. v), TLC 5.16 L/78% (ref. v), DL_{CO} 4.83/54% (ref. v)
- Indicated restrictive ventilatory defect, and, moderately lowered transfer factor predominantly due to the loss of functional alveoli.

Radiology

- *Posteroanterior chest X-ray*: Bilateral reticulations, especially in the lower lobes (Fig. 7.40a, b).
- *HRCT of the lungs*: Radiological signs of possible UIP—typical subpleural linear to reticular opacities, with accentuation basally and dorsally, no honeycombing (Fig. 7.41a–e).

Bronchoalveolar Lavage

- Alveolar macrophages 78%, lymphocytes 11%, granulocytes 11%.

Autoantibody Screening

- No suspicion of systemic connective tissue disease.

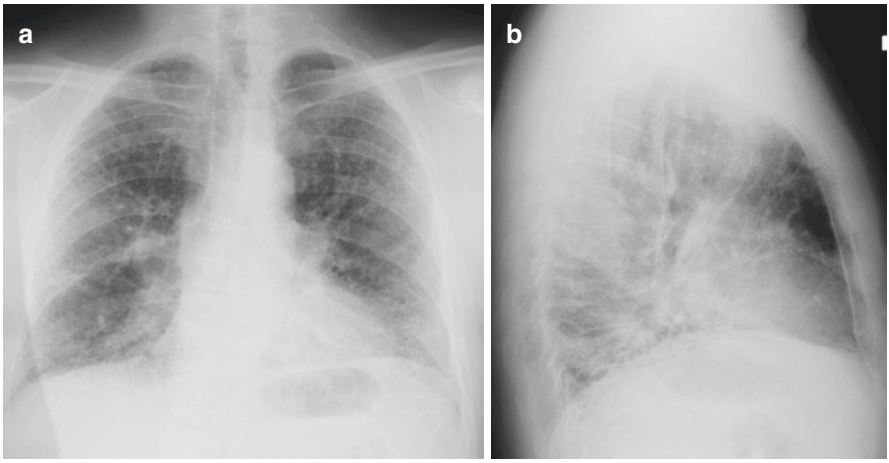


Fig. 7.40 (**a**) Posteroanterior chest X-ray: reticulations bilaterally, especially dorsally, basally. (**b**) Lateral chest X-ray: reticulations dorsally

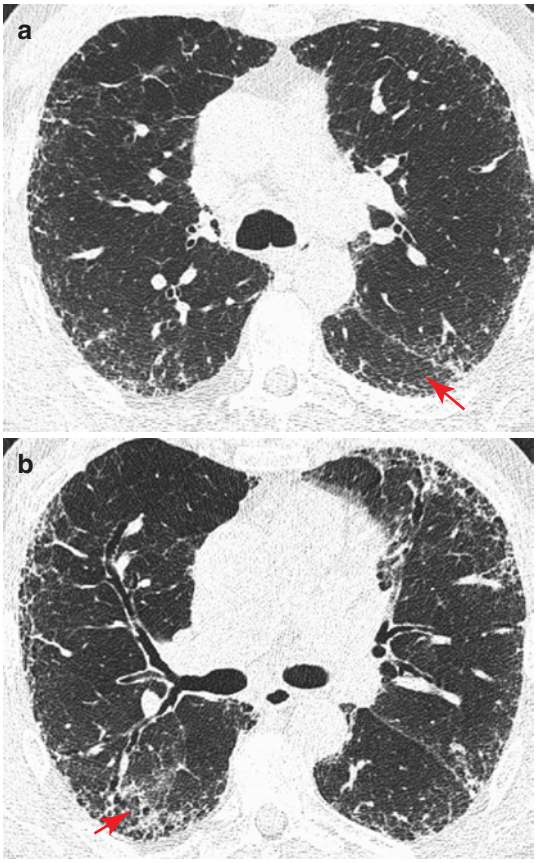


Fig. 7.41 (**a**) HRCT of the lungs: subpleural fine reticulations. (**b**) HRCT of the lungs: subpleural fine reticulations with traction bronchiectasis. (**c**) HRCT of the lungs: traction bronchiectasis and reticulations. (**d**) HRCT of the lungs (coronal reconstruction): reticulations, traction bronchiectasis and GGO in the basal parts of the lungs. (**e**) HRCT of lungs: sagittal reconstruction—bronchiectasis

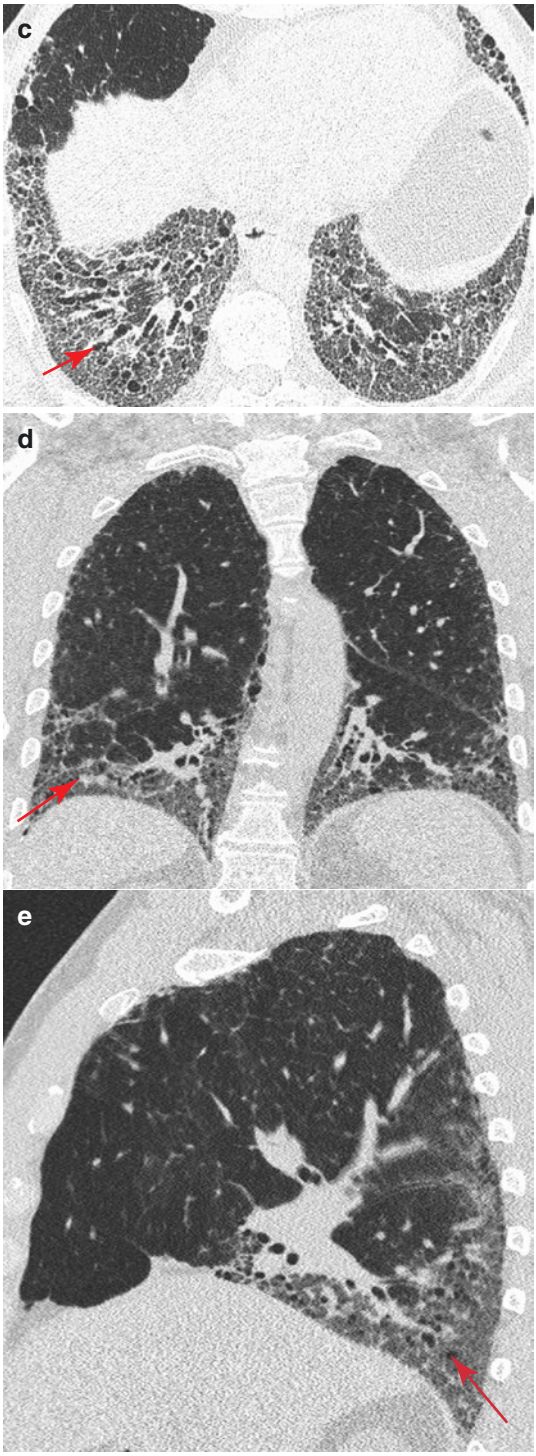


Fig. 7.41 (continued)

7.9.1 Multidisciplinary Team and Differential Diagnosis

According to the HRCT, it is a sign of fibrosis and bronchioloectasis, which is predominantly basal. There is no honeycombing present. It is necessary to perform histological verification.

Surgery—Atypical Resection of the Right Upper and Lower Lobes

- In the given sample, it reveals end-stage fibrosis of uncertain origin, and vascular changes (fibrosis and thickening of the vascular walls, especially in the intima) are apparent. It is necessary to consider the possibility of a previous vasculitis.

Auxiliary Examinations

- Nephrological Examination—Normal findings of the kidney during an ultrasound examination, with normal renal function. A urine sample was taken and was without proteinuria or haematuria. Autoantibodies including ANCA continue to be negative.
- Nailfold Capillaroscopy: Normal finding.
- Echocardiography: Signs of mild pulmonary hypertension, right ventricular hypertrophy, and a good systolic function of the right ventricle.
- Lung Ventilation—Perfusion Scan: Without evidence of a successive embolism.
- Spiroergometry: Load tolerance is reduced and the circulatory response to the load is minimally impaired, with reduced cardiac output dynamics. The function of the ventricles seems to be mildly reduced. The ventilation response is increased with a higher ventilation/perfusion ratio, which essentially does not decrease. Mechanical ventilation limitation is present, and the probability of pulmonary hypertension is low. The overall physical condition is reduced. The findings correspond to a clinical diagnosis where the respiratory function of the lung is affected rather than the mechanics.
- Consultation at the Pulmonary Hypertension Centre, Hemodynamics: There are no signs of pulmonary hypertension and there is a normal cardiac output.

7.9.2 Second Multidisciplinary Team with Differential Diagnosis

A histologically verified lung disease with non-specific findings. A pathological opinion is end-stage fibrosis with vascular changes, which does not exclude vasculitis. The patient was examined by a nephrologist and there is no renal pathology, and the capillaroscopy was negative. According to HRCT, there are progressive changes and the findings correspond to UIP. It is concluded that this is IPF and we recommend antifibrotic treatment.

7.9.3 Conclusion

The radiological findings are compatible with possible UIP (no honeycombing), histologically probable UIP, and clinically idiopathic pulmonary fibrosis (IPF).

Note

- Since the benefits of antifibrotic treatment have been proved so far only in patients with IPF, in patients with a radiological and/or histological image of UIP it is especially necessary to exclude all diseases caused by exogenous agents, and the pulmonary manifestation of SCTD.
- It is not an error to discuss the case of a patient repeatedly after completing the necessary examinations; on the contrary, it may be a mistake to overlook the pathological findings of another organ system, which is usually typical in patients with vasculitis and other SCTD.

7.9.4 Idiopathic Pulmonary Fibrosis—What We Should Consider in Differential Diagnosis

1. Interstitial pneumonia with autoimmune features (IPAF): An ILD with concurrent signs of SCTD, where not all the criteria according to which the disease can be classified as SCTD with pulmonary disease are fulfilled—usually more apparent are consolidations (Fig. 7.42).
2. Systemic connective tissue disease with pulmonary disease: necessary knowledge of the past medical history (Fig. 7.43).
3. Fibrosing form of NSIP: GGO and reticulation on HRCT. A differential diagnosis from UIP can be very difficult (Fig. 7.44).

   These would also come into consideration: chronic HP and asbestosis—see the relevant case reports.

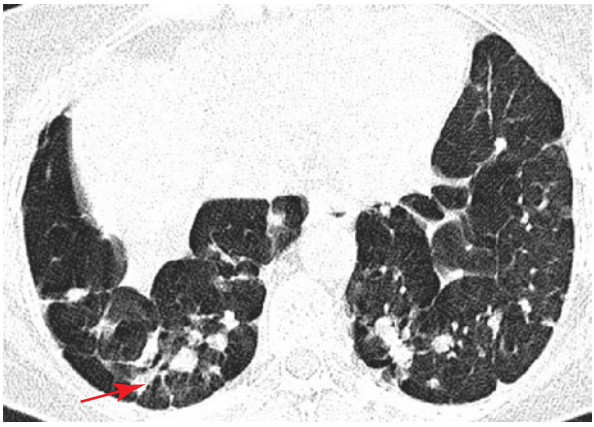


Fig. 7.42 Interstitial pneumonia with autoimmune features (IPAF): consolidations perivascularly

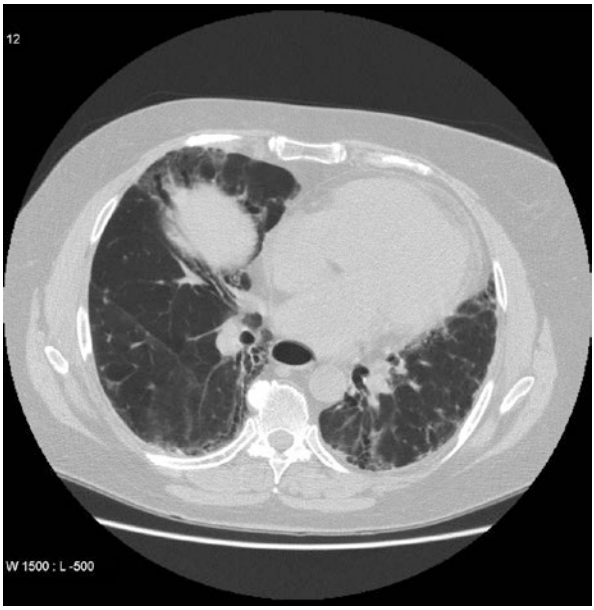


Fig. 7.43 Systemic connective tissue disease with pulmonary disease: reticulations

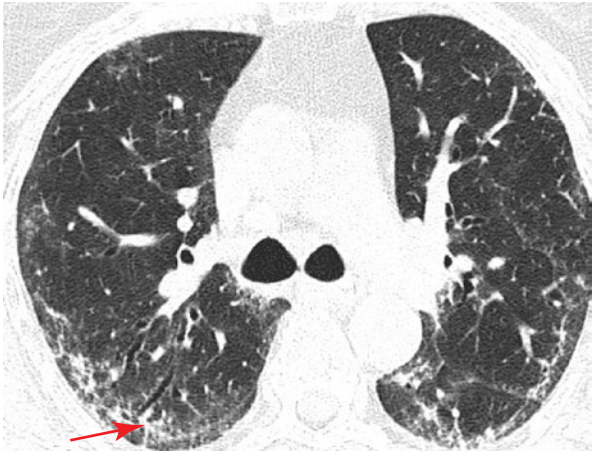


Fig. 7.44 NSIP: reticulations, traction bronchiectasis

7.10 Idiopathic Pulmonary Fibrosis II

Eva Kocova and Vladimir Bartos

Male, 52 years old.

The patient presents with a 1-year history of exertional dyspnoea.

Medical History

- Psoriasis since the age of 5
- Arterial hypertension

Occupational History and Exposure

- Vehicle mechanic
- Lives with family in a block of flats, without animals
- Smoking history: 25 cigarettes a day between the ages of 20 and 42

History of Present Complaint

- Had severe bronchitis 2 years ago, and since then has had increased breathlessness during exertion, with no symptoms of coughing. At rest, he is without dyspnoea. He actively participates in sports, and his psoriasis is stabilised.

Objective Finding

- Vesicular breathing, basal crepitations, and nail clubbing.

Examination

Lung Functional Tests

- FVC 3.33 L/78% (ref. v), VC_{max} 3.76 L/85% (ref. v), TLC 5.76 L/86% (ref. v), DL_{CO} 7.55/73% (ref. v)
- A mild reduction in forced vital capacity; the resting maximum capacity is normal. The patient remains without an expressed restrictive ventilatory disorder, and the transfer factor for CO is slightly restricted

Radiology

- *Posteroanterior and lateral chest X-ray*: Description available only: coarsened pulmonary markings.
- *HRCT of the lungs*: Multiple bilateral subpleural reticulations. Changes have an expressed craniocaudal gradient—most changes are located basally. Fibrosis with a reduction of the lung volume, especially of the lower lobes, with a shift of the interlobar fissures. Traction bronchiectasis, and honeycombing (Fig. 7.45a–d).

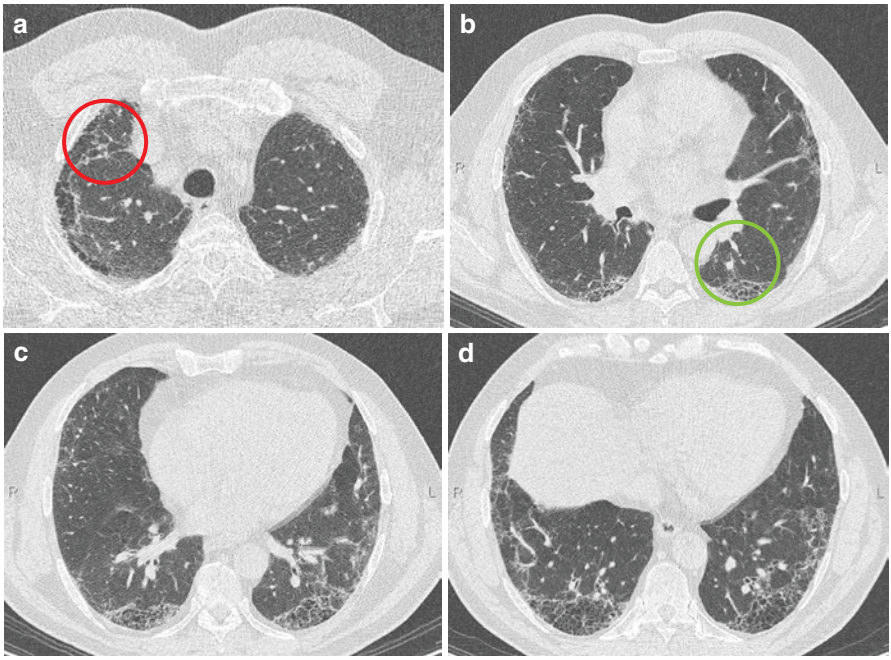


Fig. 7.45 (**a**) HRCT of the lungs: bilateral and subpleural reticulations, honeycombing in the right upper lobe. (**b**) HRCT of the lungs: bilateral and subpleural reticulations, honeycombing in both lungs in dorsal parts. (**c**) HRCT of the lungs: honeycombing dorsally and bilaterally, some reticulations. (**d**) HRCT of the lungs: reticulations and honeycombing, with maximum changes dorsobasally and bilaterally

7.10.1 Multidisciplinary Team and Differential Diagnosis

HRCT signs of a typical picture of usual interstitial pneumonia (UIP)—reticulations with maximum basal and subpleural distribution, traction bronchiectasis, honeycombing, and the absence of patterns not corresponding to UIP (see Table 5.1).

SCTD was excluded by the rheumatologist, and external factors of the disease are not confirmed.

The conclusion of the MDT: Clinically and radiologically, it is probably idiopathic pulmonary fibrosis. Bronchoalveolar lavage and transbronchial biopsy are recommended.

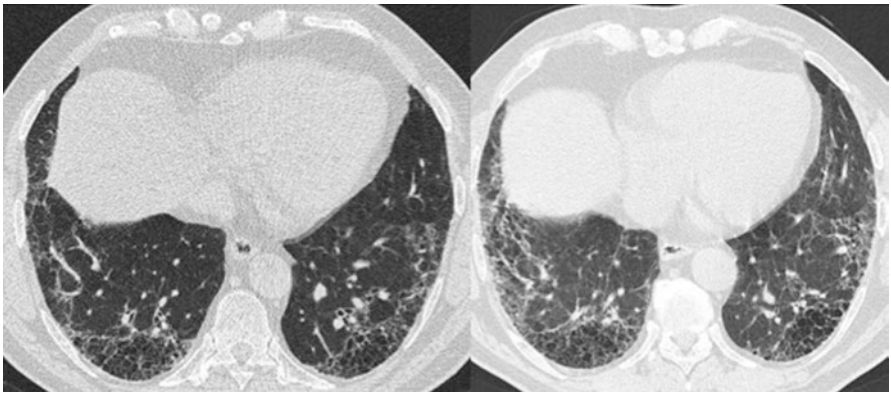


Fig. 7.46 CT in the time of diagnosis and 5 years after the diagnosis with the progression of fibrotic changes

Bronchoscopy, Bronchoalveolar Lavage, TBB

- *BAL*: Rich cell material, 87% macrophages, 6% lymphocytes, 7% neutrophils.
- *TBB*: Fibrotic lesions. No malignant structures or structures of granulomatous inflammation found.

7.10.2 Conclusion

- Radiological findings are compatible with UIP and clinically correlate with IPF.
- During biological therapy of IPF, there was a slow progression of the disease state. A CT scan performed 5 years after diagnosis revealed the progression of fibrotic changes (Fig. 7.46).

7.10.3 Idiopathic Pulmonary Fibrosis

To determine the diagnosis of IPF, a combination of clinical and radiological and eventually histopathological investigations are required. If other causes of the ILD are excluded, and the pathological changes indicated radiologically are typical of UIP (see Table 5.1), then there is no need for histological verification.

If the radiological image is not typical, then the patient should undergo histopathological verification with a lung biopsy. The diagnosis of IPF is then determined on the basis of a combination of radiological and histopathological findings (Table 7.1).

Table 7.1 Specific combinations of HRCT and histopathological (surgical lung biopsy) UIP patterns in patients with pulmonary biopsy. According to Vašáková M, Šterclová M. Idiopathic pulmonary fibrosis—recommended procedure for diagnosis, treatment, and monitoring. www.pneumologie.cz

HRCT image	Histopathological image	IPF diagnosis
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis	Yes
	It is not UIP	No
Possible UIP	UIP Probable UIP	Yes
	Possible UIP Non-classifiable fibrosis	Probable
	It is not UIP	No
Inconsistent UIP	UIP	possible
	Probable UIP Possible UIP Non-classifiable fibrosis It is not UIP	No

7.10.4 Criteria for the Diagnosis of Idiopathic Pulmonary Fibrosis

- Exclusion of other causes of ILD (home and occupational exposure, SCTD, and medication toxicity).
- The presence of an HRCT pattern of UIP in patients without a pulmonary biopsy.
- Specific combinations of HRCT and histopathological (surgical lung biopsy) UIP patterns in patients with a lung biopsy.

A lung biopsy should be indicated with regard to the patient's overall condition and his lung function. If a histopathological verification cannot be performed, it is necessary to rely on the combination of clinical and radiological images, even if the radiological signs present possible UIP.

Note

- The signs of UIP on HRCT can similarly present in idiopathic pulmonary fibrosis, asbestosis, and in SCTD. HRCT signs can indicate signs of a typical UIP, possible UIP, or changes that do not correlate with UIP. Possible UIP and image which do not correlate with UIP the pathological processes should be verified by biopsy (cryobiopsy or VATS pulmonary biopsy).
- CAVE—large lesions of GGO may be present in UIP at the same time as an acute exacerbation of an underlying disease or acute infection!

7.10.5 Idiopathic Pulmonary Fibrosis—What We Should Consider in Differential Diagnosis

1. Drug-induced lung disease: A history of pneumotoxic medication (Fig. 7.47).
2. Asbestosis: A history of asbestos exposure, similar signs as UIP often with subpleural plaques or pseudoplaques (Fig. 7.48).
3. Chronic hypersensitivity pneumonitis: Suspected or proven exposure to organic antigens, fibrosis on a CT scan, air trapping and centrilobular nodules (Fig. 7.49).
4. Fibrosing sarcoidosis: Predilections in the upper lung fields, and perilymphatic nodules (Fig. 7.50).
5. Usual interstitial pneumonia in systemic connective tissue disease: Signs of UIP patterns, with SCTD in the past medical history (Fig. 7.51).

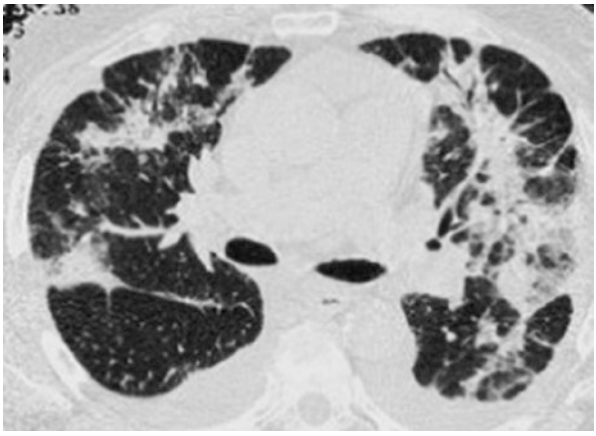


Fig. 7.47 Drug-induced lung disease: patchy consolidations and reticulations

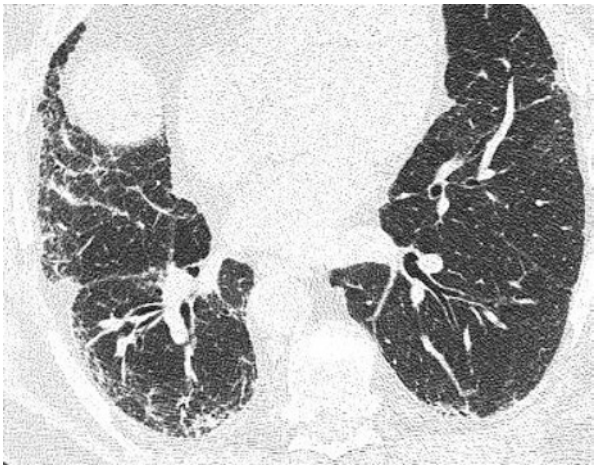


Fig. 7.48 Asbestosis: subpleural reticulations, pleural plaques

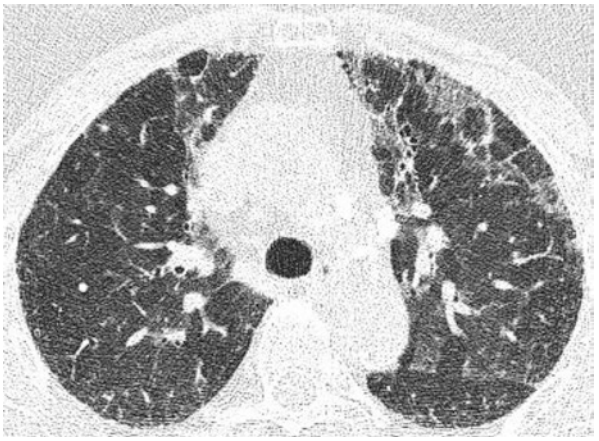


Fig. 7.49 Chronic hypersensitivity pneumonitis: ground glass opacities, thickening of peribronchovascular interstitium

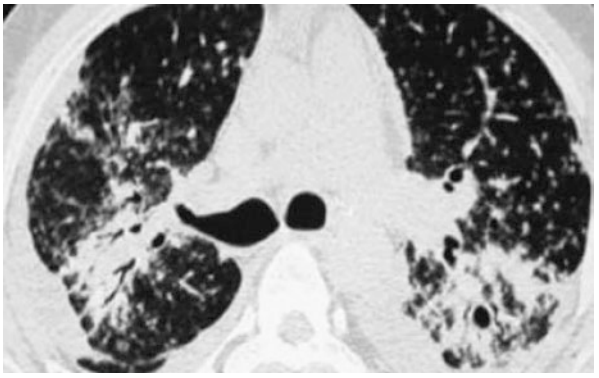


Fig. 7.50 Fibrosing sarcoidosis: Perilymphatic nodules and consolidations with nodules in the periphery ("galaxy sign"), hilar apicalisation

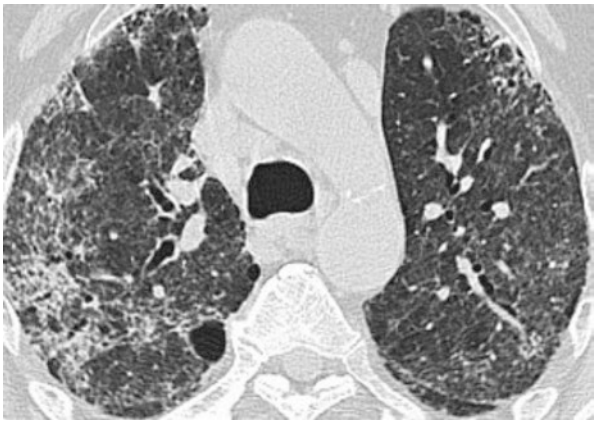


Fig. 7.51 Usual interstitial pneumonia in systemic connective tissue disease: UIP patterns—reticulations and honeycombing in subpleural areas

7.11 Radiation Pneumonitis

Martina Sterclova and Jana Votrubova

Female, 80 years old.

Patient presenting with 2-month lasting symptoms of increased body temperatures and exertional dyspnoea.

Medical History

- Arterial hypertension
- Hypothyroidism
- Mastectomy secondary to right breast carcinoma followed by radiotherapy (terminated 3 months before the development of the patient's symptoms) and hormonal therapy

Occupational History and Exposure

- Pensioner, previously worked in a sawmill—cutting wood on a circular saw—dusty environment
- Lives alone in a flat with no pets
- Smoking history: lifelong non-smoker

History of Present Complaint

- Approximately 3 months post radiotherapy for breast cancer the patient was pyrexial and had dyspnoea. She was first treated as an outpatient and sent home with antibiotics. Due to symptoms not resolving significantly, she was recommended for further examinations. She has no cough, but complains of dyspnoea during moderate exertion. She has put on 2 kg of weight and has increased perspiration. From an oncological perspective, the cancer is in complete remission.

Objective Finding

- Vesicular breathing, with left basal inspiratory rales.

Examination

Lung Functional Tests

- FVC 1.21 L/52% (ref. v), FEV_1 1.16 L/61% (ref. v), FEV_1/FVC 96%
- Estimated values. The patient is unable to manage manoeuvres due to dyspnoea, and she cannot manage the test for transfer factor. The findings indicate a moderate reduction in vital capacity

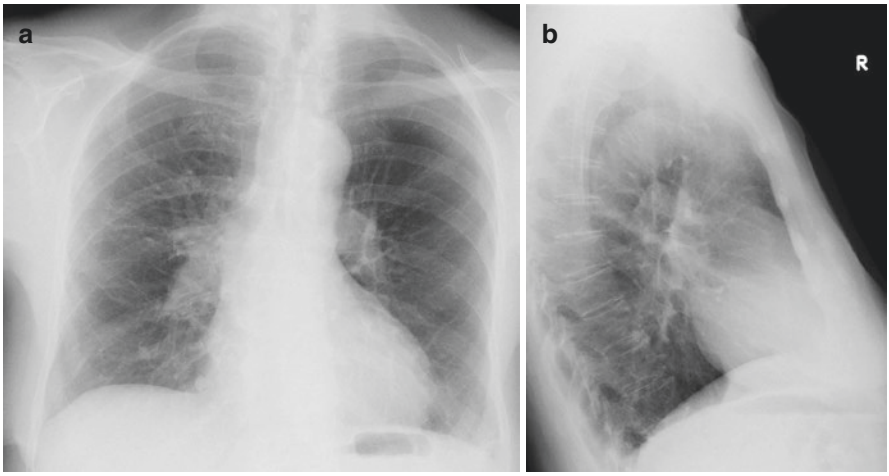


Fig. 7.52 (**a**) Posteroanterior chest X-ray: strip-like to cloud-like shadows in the right lung. The left lobe shows normal transparency. (**b**) Lateral chest X-ray: patchy shadows in the upper lobes

Radiology

- *Posteroanterior and lateral chest X-ray*: Significant lateral changes, with a finding of a strip-like to cloud-like consolidation in the right pulmonary lobe (Fig. 7.52a, b).
- *HRCT of the lungs*: Subpleural fine fibrous strips with a tendency to retract, in the right pulmonary lobe. The left pulmonary lobe is without any special abnormalities (Fig. 7.53a, b).

Autoantibody Screening

- ANA neg., ENA neg., RF neg.

Bronchoalveolar Lavage

- Alveolar macrophages 68%, neutrophils 5%, lymphocytes 24%, and eosinophils 3%.

7.11.1 Multidisciplinary Team with Differential Diagnosis

A patient with an interstitial lung disease that is connected to the time of external radioablation therapy of the right breast for malignancy. Antibiotic treatment was without effect, and according to the oncologist, the cancer is in complete remission. SCTD is unlikely, and a history of exposure to organic inhaled antigens is missing. It is likely to be radiation pneumonitis, and the HRCT corresponds with these findings.

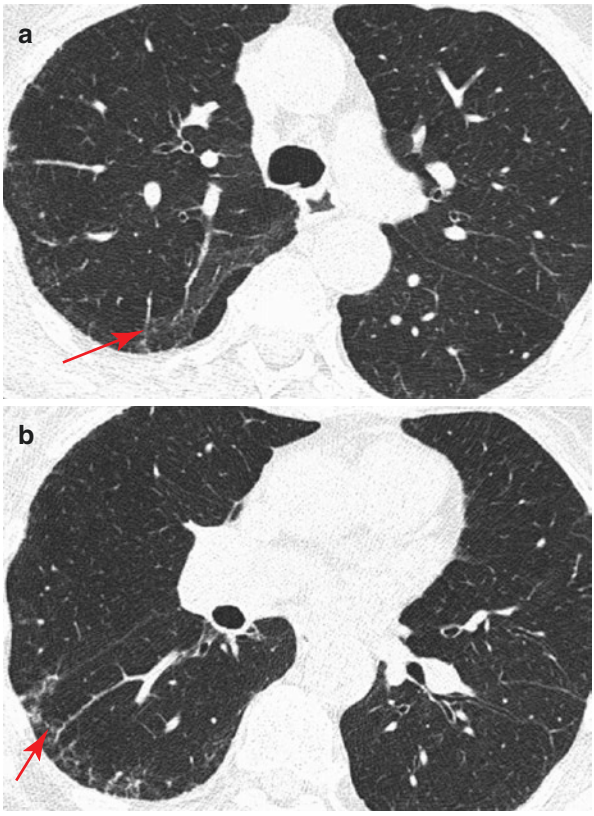


Fig. 7.53 (**a**, **b**) HRCT of the lungs: reticulations subpleurally in the right lobe

7.11.2 Conclusion

Radiation fibrosis with predominance on the right according to the chest HRCT. Systemic corticosteroid therapy was initiated, and at the time, with a good clinical effect.

Lung functional tests (5 years after the diagnosis, 4 years post systemic corticosteroid therapy).

- FVC 2.16 L/87% (ref. v), VC_{max} 2.85 L/115% (ref. v), TLC 4.18 L/83% (ref. v), DL_{CO} 3.88 mmol/kPa/min/59% (ref. v)
- Slightly reduced transfer factor, otherwise normal vital capacity, with no restrictive ventilatory disorder

7.11.3 Radiation Pneumonitis

Radiation pneumonitis is a diagnosis of exclusion—i.e. it is first necessary to eliminate infectious complications of anticancer therapy, cardiovascular disease, and

progression of the underlying cancerous disease in the patient with a history of chest radiotherapy. Patients who have undergone whole-body irradiation (e.g. within the treatment of haematological disease, typically before bone marrow transplant), and also candidates of conventional fractionation therapy, may be affected. We can also find post-radiation lung disease in patients who have undergone stereotactic radiotherapy (SABR/SBRT) for bronchogenic carcinoma. In these patients, it is necessary to exclude in differential diagnosis in particular relapse or progression of the underlying disease, especially in patients who may benefit from further treatment. If the pulmonary disease develops within 6 months after the termination of radiotherapy, we talk of early damage, then radiologically on HRCT are encountered GGO and/or consolidations (as a diffuse damage is considered to be lesion larger than 5 cm in diameter, below this we are talking about nodules). If post-radiation fibrosis occurs more than 6 months after radiotherapy, the nature of changes is rather scarring.

Note
The risk of development of pulmonary damage resulting from radiotherapy increases in elderly patients with a pre-existing pulmonary disease, and a tumour in the lower pulmonary lobe area. However, with pulmonary damage after radiotherapy, we can also see patients irradiated for an extrapulmonary malignancy in the chest area.

7.11.4 Radiation Pneumonitis—What We Should Consider in Differential Diagnosis

1. Hypersensitivity Pneumonitis: The chronic stage of this disease is characterised by thickened interlobular septa, while the acute stage of the disease is characterized by increased GGO (Fig. 7.54).
2. Malignant tumorous disease lymphangitic carcinomatosis—thickening of interlobular septa with random nodules (Fig. 7.55).

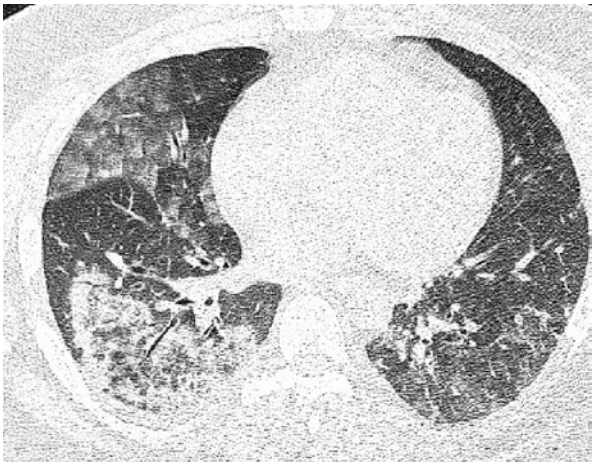


Fig. 7.54 Hypersensitivity Pneumonitis: thickened interlobular septa and fine perivascular fibrous strips changes

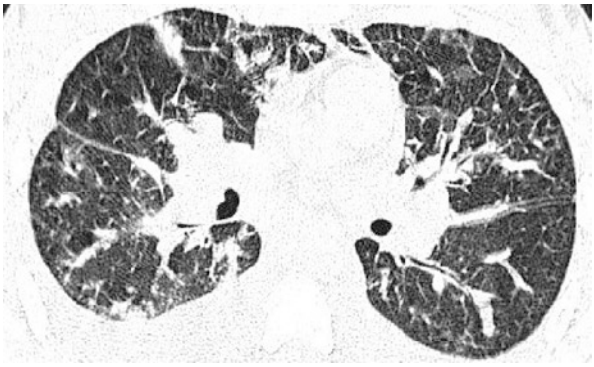


Fig. 7.55 Carcinomatous lymphangitis—reticulations and random nodules, hilar lymphadenopathy

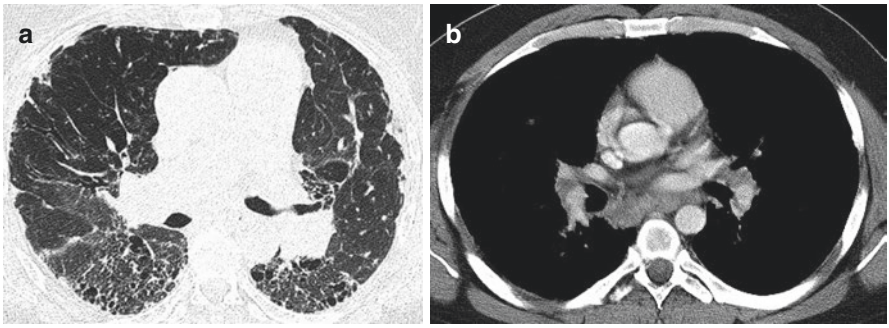


Fig. 7.56 (**a**) Fibrosing sarcoidosis: reticulations, hilar apicalisation, honeycombing. (**b**) Fibrosing sarcoidosis (mediastinal window): symmetrically enlarged hilar lymph nodes and lymph nodes below the carina of the trachea

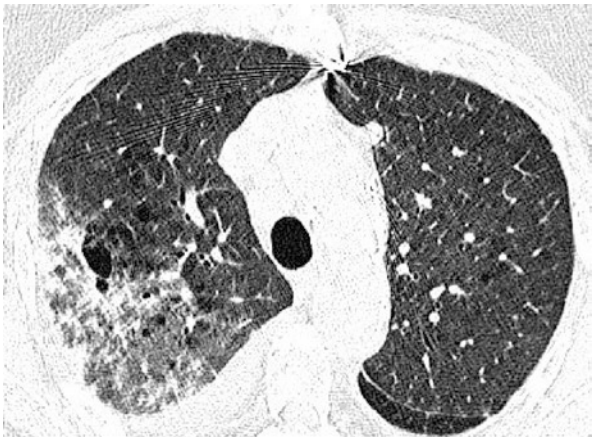


Fig. 7.57 Drug-induced disorder (Amiodarone lung): GGO, and fine consolidations with pleural reaction prevail

3. Fibrosing sarcoidosis: In the lung window, typically affects bilaterally with fine fibrous strips peribronchially (Fig. 7.56a, b).
4. Drug-induced disorder: Amiodarone—GGO, and fine consolidations with pleural reaction prevail (Fig. 7.57).

7.12 Idiopathic Pleuroparenchymal Fibroelastosis

Martina Sterclova, Jana Votrubova, and Eva Kocova

Female, 39 years old.

The patient presents with repeated respiratory infections, pleurodynia, and dyspnoea and weight loss.

Medical History

- During childhood—repeated pneumonia and tonsillitis, and has had a tonsillectomy
- Diagnosed with asthma since primary school, polyvalent allergies—pollen, dust, mites, cephalosporin antibiotics
- Operation of paranasal sinuses for cysts at 17 years of age

Occupational History and Exposure

- Doctor, lives in a dry flat, with no animals
- Smoking history: lifelong non-smoker
- Until now without permanent medication

History of Present Complaint

- Last year, she had bronchitis, followed by pleurodynia, which lasted for about half a year. She began to lose weight. She had another respiratory infection with a cough and occasional haemoptysis, and chest pain occurred again. Now she gets short of breath at minimal exertion, but she does not complain of a cough.

Objective Finding

- Cachectic, irregularly shaped pigment stains of coffee colour on the abdomen, vesicular breathing with bilateral mild rales and wheeze.

Examination

Lung Functional Tests

- FVC 1.09 L/28% (ref. v), VC_{max} 1.09 L/27% (ref. v), TLC 2.97 L/50% (ref. v), DL_{CO} 3.04/31% (ref. v)
- Severely reduced vital capacity, severe restrictive ventilatory disorder, heavily reduced transfer factor

Radiology

- *Posteroanterior and lateral chest X-ray*: Bilateral patchy regions of consolidation of the pulmonary parenchyma, with pleural thickening in the upper pulmonary

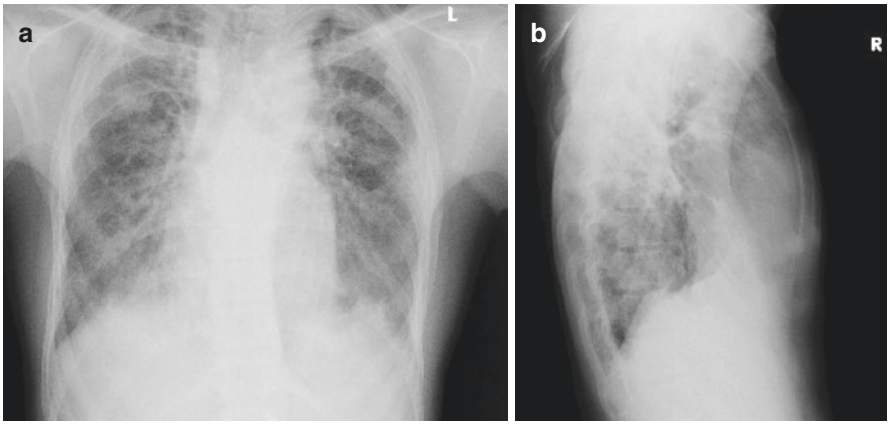


Fig. 7.58 (**a**) Posteroanterior chest X-ray: bilateral dispersed regions of patchy shadows, pleural thickening in the upper pulmonary fields peripherally. (**b**) Lateral chest X-ray: chest shortening in the anteroposterior diameter—platythorax

fields peripherally. In the lateral view, there is a truncation of the chest in the anteroposterior direction—platythorax (Fig. 7.58a, b).

- *HRCT of the lungs*: Typical irregular bilateral visceral pleural thickening with subpleural fibrosis, parenchymal distortion, and regions of consolidation forming triangular impressions ("wedge") with the inverted bases towards the pleura and the tip towards the hilum (Fig. 7.59a–c).

Bronchoalveolar Lavage

- Alveolar macrophages 64%, lymphocytes 36%, numerous foamy macrophages.

Autoimmunity Screening and Screening of Exposure—Specific IgG Serum

- ANA neg., ENA neg., RF neg., anti-dsDNA neg., ANCA neg., high levels of specific IgG against mites (up to >200 mg/L), fungi (191 mg/L), and bird feathers (125 mg/L).

Auxiliary Examination and Tests

- Severe microcytic hypochromic anaemia (Hb 67 g/l), sideropenia, and no signs of humoral or cellular immunodeficiency.

Addition to a Medical History Based on the Result of the Examinations

- After child birth, the patient was administered transfusions. She was known to have chronic anaemia and takes iron supplementations. She tends to have diarrhoea after eating fresh bread and also has heartburn. Her house is being repaired, and there is a damp wall. Her symptoms are worse on Mondays when she is at work. One floor down, on the ledge, usually there are pigeons nesting.

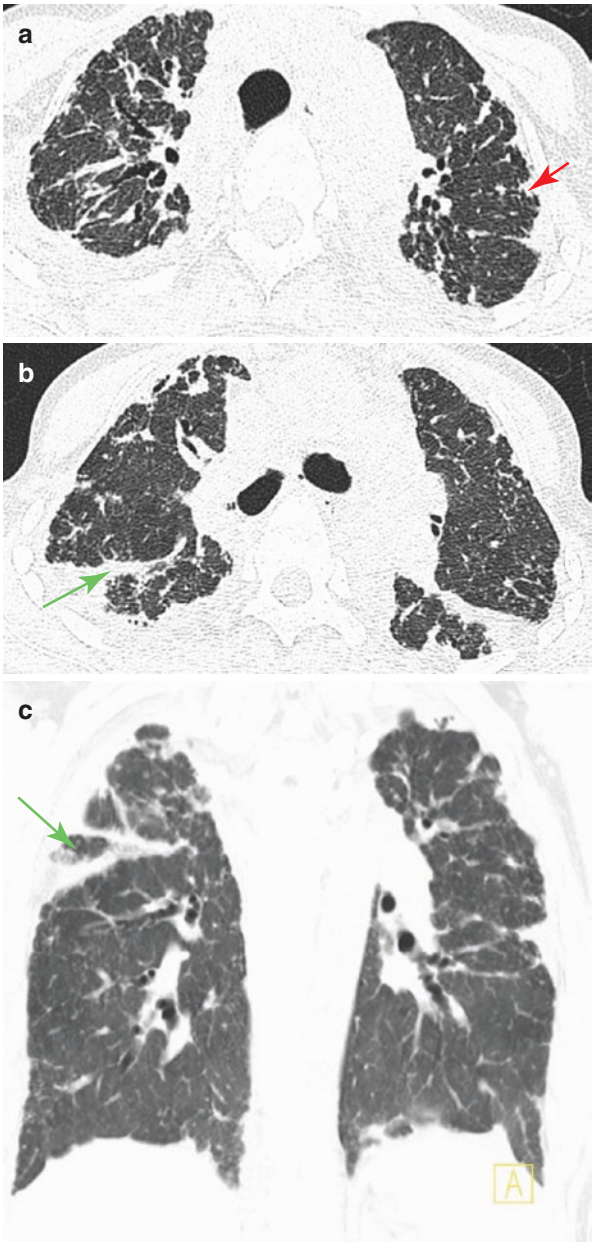


Fig. 7.59 (**a**) HRCT of the lungs: typical irregular visceral pleural thickening bilaterally with subpleural fibrosis, distortion of the parenchyma and regions of consolidation creating the impression of triangles ("wedge") with the inverted bases towards the pleura and the tip towards the hilum. (**b**) HRCT of the lungs (scan above the carina): typical irregular visceral pleural thickening with subpleural fibrosis, distortion of the parenchyma and regions of consolidation creating the impression of triangles ("wedge") with the inverted bases towards the pleura and the tip towards the hilum. (**c**) HRCT of the lungs (coronal reconstruction): regions of consolidation creating the impression of triangles ("wedge") with the inverted bases towards the pleura

7.12.1 Multidisciplinary Team and Differential Diagnosis

Patient with an interstitial lung disease, with a combination of chronic changes more of a COP image. This may be HP or chronic eosinophilic pneumonia. A VATS biopsy is required.

VATS and Histology

- Sections of fairly extensive and confluent fibrosis, with regions of minor chronic inflammatory lymphoid cellularisation built on areas where polyps of Masson develop. Granulomatous formations, vasculitis or tumours are not found, and segments of calcification are apparent. Please consider a systemic connective tissue disease.

Auxiliary Examinations

- Rheumatological examination: The rheumatological examination does not clearly indicate a suspected systemic connective tissue disease.
- Haematological examination: This is iron-deficient anaemia; the patient either loses or does not absorb iron.

7.12.1.1 Conclusion 1

- An ILD with features of fibrosis and organising pneumonia with pleural involvement. Due to skin manifestations, failure to thrive, and diarrhoea, it could be a SCTD. The participation of HP cannot be excluded.
- Systemic corticosteroid therapy and a gastroenterological examination recommended.

Gastroenterological Examination

- Enterobiopsy confirmed the suspicion of coeliac disease, and a gluten-free diet was initiated. The patient did not start the corticosteroid treatment and came for a check-up after 8 months of worsening dyspnoea, and manifested hypercapnic respiratory insufficiency—arterial blood gas (without O_2 supplementation): pH 7.375, pCO_2 7.72 kPa, pO_2 6.46 kPa.

Histology from VATS—Revision Finding

- In addition to the described changes, an accentuation of fibrotic changes is apparent subpleurally and partly also centrilobularly. After completing the histochemical examinations, we find some prominent representation of elastic fibres. Their architecture in some regions is completely disorganised. The ratio of elastic to collagenous fibres fluctuates, and rarely even reaches 80%.

7.12.2 Multidisciplinary Team and Differential Diagnosis

The patient has an ILD with pleural thickening, and in 2013, histologically confirmed with unspecified fibrosis. At that time, there was progression, significant thickening of the pleura, asthenia and a flat chest. Radiological findings are compatible with pleuroparenchymal fibroelastosis (PPFE), and the second reading of histology is inconsistent with this diagnosis. The use of systemic corticosteroid therapy will not bring any beneficial effect and the treatment can be discontinued.

7.12.2.1 Conclusion 2

- Pleuroparenchymal fibroelastosis, histologically confirmed, with hypercapnic respiratory insufficiency.
- The patient was examined and placed on a waiting list for a pulmonary transplant.

7.12.3 Pleuroparenchymal Fibroelastosis

Pleuroparenchymal fibroelastosis (PPFE) is a rare disease, originally described in 1992 as so-called Amitani's disease. It affects non-smokers and individuals with a low body mass index, causing a significant decline of lung functional tests and leading to platythorax—anteroposterior flattening of the thorax. Typical HRCT images are irregular pleural thickening predominantly involving the upper lobes, hilar apicalisation and wedge-shaped opacities extending from the pleura. In the lower lobes, we can radiologically find the UIP image. The primary histological features are dense intraalveolar fibrosis, fibrous visceral pleura thickening, and fibrosis of adjacent tissue, with a dominating presentation of elastic fibres over collagenous fibres. The disease may be idiopathic, but more often we encounter similar findings in patients after lung or haematopoietic cell transplant, or in patients who have been treated with chemotherapy in the past.

Note

- Pleuroparenchymal fibroelastosis is considered in the differential diagnostics of fibrosing pulmonary diseases with simultaneous pleural thickening in the upper pulmonary lobes.
- Since patients with PPFE more often have respiratory infections, which can negatively affect the course of the disease as the therapy is based primarily on the consistent prevention and treatment of infections, eventually an early inclusion in the transplant program.

7.12.4 Idiopathic Pleuroparenchymal Fibroelastosis—What We Should Consider in Differential Diagnosis

1. Drug-induced pulmonary disorder: History of using pneumotoxic medication (Fig. 7.60).
2. Radiation pneumonitis: History of irradiation of the chest (Fig. 7.61).

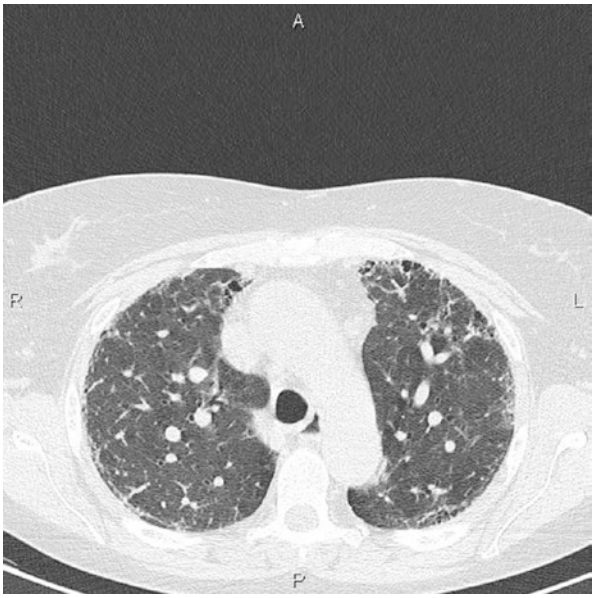


Fig. 7.60 Drug-induced pulmonary disease: subpleural reticulations

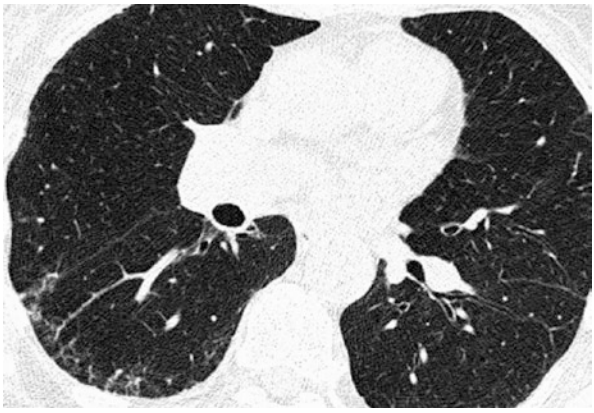


Fig. 7.61 Radiation pneumonitis: fine subpleural reticulations

3. Sarcoidosis: In the late stage, differential diagnosis can be difficult without knowledge of the past medical history. Perilymphatic nodules, calcified nodes in the mediastinum and hila can be apparent (Fig. 7.62).

These would also come into consideration in the differential diagnostics: systemic connective tissue disease or asbestosis.

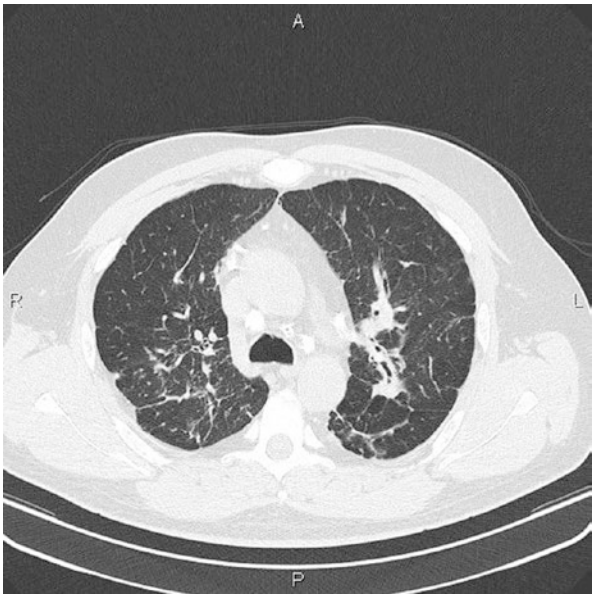


Fig. 7.62 Sarcoidosis: Small perilymphatic nodules, calcified lymph nodes in the mediastinum

7.13 Interstitial Lung Disease with Fluidothorax

Martina Sterclova, Jana Votrubova

Female, 62 years old.
Presenting with bilateral fluidothorax of unclear aetiology, subfebrile, with exertional dyspnoea.

Medical History

- Arterial hypertension—treated with losartan, metoprolol, amlodipine, furosemide
- Hyperlipoproteinemia—taking fenofibrate
- Osteochondrosis of C6 and C7 intervertebral discs, and cervical spondylosis
- Gastroduodenal ulcerative disease, currently in remission, taking omeprazole

Occupational History and Exposure

- Used to work as an accountant, lives in a flat with her mother whom she takes care of
- Smoking history: lifelong non-smoker
- She has never had pets

History of Present Complaint

- The patient gets short of breath during exertion for 2 months, coughs, and is subfebrile. She has previously been hospitalised in a different hospital and was diagnosed with bilateral fluidothorax, the cause was not unidentified. The current condition of the patient has worsened over time and she presents with pain and bilateral swelling of the knees and small joints of the hand, and weight loss. She has come in for hospitalisation.

Previous Hospitalisation Investigations

- Ventilation/perfusion scan is without evidence of pulmonary embolism. An echocardiograph identified a haemodynamically insignificant fluidopericardium. CT of the abdomen revealed ascites, and a colonoscopy was with evidence of benign ulceration in the caecum, with histologically confirmed focal active colitis—a differential diagnosis is necessary to exclude Crohn's disease. A gastroscopy was negative. Pleural puncture detected no oncologically suspicious elements in the collected material.

Objective Finding

- Bilateral vesicular breathing, and reduced air entry on the right base and on the left up to 1/3 of the hemithorax.

Examination

Radiology

- *Hand and Knee Joint X-ray*: Discrete narrowing of the interphalangeal joint spaces of the fingers, with no other skeletal degenerative changes. The joint spaces of the knee are symmetrical, without signs of damage or degenerative changes.
- *HRCT of the chest*: Bilateral pleural effusion with regions of compressed lung tissue. In the remaining airy parenchyma, there are very discreet changes of fine thickening of the interlobular septa—linear opacities. The soft tissue window manifests fine pleura without calcifications or nodular thickening. In addition to pleural effusion, there is also identified pericardial effusion. There is a significantly high proportion of pleural effusion in regard to the affected lung (Fig. 7.63a, b).

Thoracocentesis

- Practically a non-cellular slide, with only a slight capture of lymphoid elements. Biochemically, it is an exudate.

Bronchoalveolar Lavage

- Few cells, mostly damaged, impurified cilia cells—invalid.

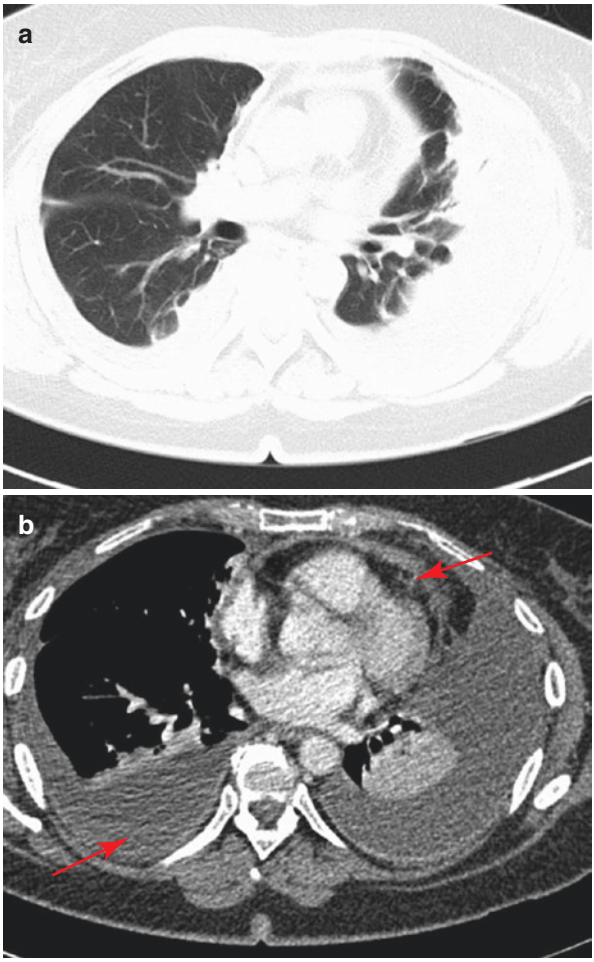


Fig. 7.63 (**a**) HRCT of the lung (lung window): bilateral pleural effusion with regions of non-airy, compressed lung tissue. In the remaining airy parenchyma, very discreet changes—fine thickening of interlobular septa and fine linear opacities. (**b**) HRCT of the lung (mediastinal window): pleura without calcifications or nodulations. In addition to pleural effusion, there is also pericardial effusion. There is a significantly higher proportion of pleural effusion in regard to the affected lung

Autoantibody Screening

- ANA is on the borderline at 1:80 titre, positive anti-histone antibodies, otherwise anti-dsDNA negative, RF negative, aCCP negative, ASCA negative, AMA negative, ANCA negative, anti GBM negative, antibodies against TTG and endomysium negative. No leukopenia identified.
- The functional examination was not performed—the patient was unable to perform required manoeuvres, due to dyspnoea.

Rheumatological Consultation

- Currently, a SCTD of systemic lupus type cannot be ruled out, although the patient does not yet meet the necessary diagnostic criteria.

Additional Examinations

- Urinalysis and sedimentation tests were without haematuria, and the 24-h urine protein test was within the standard range. Laboratory findings identified mild anaemia, thrombocytopenia, and a slight elevation in liver function tests.

7.13.1 Multidisciplinary Team and Conclusion 1

- Bilateral recurrent fluidothorax in polyserositis—probably due to an SCTD—systemic lupus erythematosus.
- Systemic corticosteroid therapy was initiated and the condition of the patient improved, with the effusions receding. The patient is afebrile, without joint pain, and the liver function tests have also improved.
- Six months later the rheumatologist discontinued the treatment, as the patient had no positive autoantibodies, and diagnosed the case as a relapse of previous parainfectious polyserositis.
- Two months after discontinuation of systemic corticosteroid therapy, the patient had symptoms of diarrhoea, weight loss, joint pain, elevation of inflammatory markers (ESR and CRP), and a moderate fluidothorax on the left according to the CT and chest X-ray. The colonoscopy was re-performed and the findings did not indicate idiopathic intestinal inflammation. Facial exanthema also appeared. With laboratory tests positive for histone autoantibodies, ANA and ANCA, a rheumatologist diagnosed the case as systemic lupus erythematosus.

7.13.2 Conclusion 2

- Systemic lupus erythematosus affecting serous membranes, skin involvement, arthritis, and suspectively even with a liver disorder. Laboratory tests are positive for histone autoantibodies, anaemia, and thrombocytopenia.
- Combined immunosuppressive treatment with systemic corticosteroids and azathioprine was initiated.

7.13.3 Interstitial Lung Disease Combined with Pleural Disease

Within the group of ILD, SCTD is usually linked to pleural disorders, especially rheumatoid arthritis, where a pulmonary disease could precede joint symptoms in up to 20% of patients (Table 7.2). Autopsy studies in patients with systemic lupus erythematosus have shown fluidothorax in up to 93% (Fig. 7.64).

ILD in combination with fluidothorax can also be associated with a drug-induced lung disorder (associated with nitrofurantoin, methotrexate, and amiodarone or IL-2 treatment).

The effusion may accompany a pulmonary disease in lymphangioleiomyomatosis (in 13–28% of patients in the form of chylothorax) or chronic eosinophilic

Table 7.2 Interstitial lung disease with pleural effusions in systemic connective tissue diseases

Nosological unit	Type of disorder
Rheumatoid arthritis	Mostly serous effusions, biochemically exudative, cytologically monocytes dominate; in 80% of the cases a low pH and glucose level; risk of developing sterile empyema, rarely pseudochylothorax
Systemic lupus erythematosus	Serous effusions, biochemically exudative, cytologically mononucleocytes dominate; if the effusion occurs acutely, neutrophils dominate; low pH and glucose level in 20% of cases
Systemic scleroderma	Effusions rarely
Polymyositis–dermatomyositis	Exudative small effusions
Mixed connective tissue disease	Effusions together with an interstitial lung disorder are rare

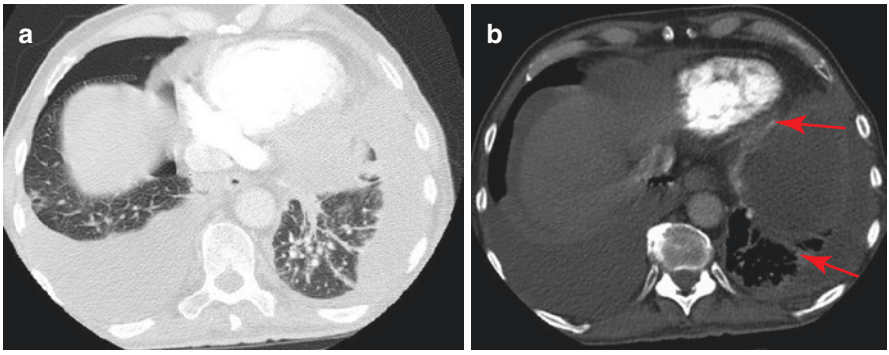


Fig. 7.64 (**a**) HRCT of the lung (lung window): fluidothorax bilaterally, fine reticulations and small random nodules. (**b**) HRCT of the lung (mediastinal window): irregular thickening of the pleural, and in addition to the pleural effusion, an effusion under the diaphragm in the peritoneal cavity is presented

pneumonia. It may also affect patients with sarcoidosis, but in clinical practice, however, it usually does not etiologically associate with sarcoidosis as such, but rather with complications in the form of heart failure.

The combination of an ILD and the pleural involvement usually also includes patients with a history of asbestos exposure and patients with carcinomatous lymphangiopathy.

Note

- In patients with an ILD and fluidothorax, it is necessary for the differential diagnosis to consider especially systemic connective tissue disease and the damage caused in connection with previous exposure to asbestos.
- Past medical history, and sometimes monitoring the patient over time, including the response to previous treatments are important. In patients with

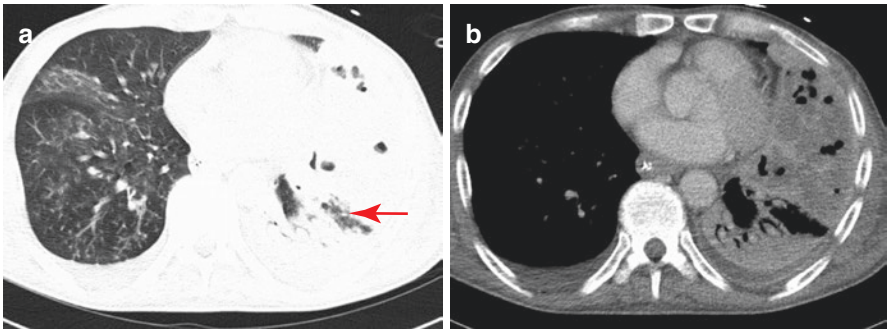


Fig. 7.65 (**a**) Infection—pleuropneumonia (lung window): Extensive heterogeneous consolidation of lung tissue with air bronchogram. In the damaged lung, there are gas bubbles and tiny hydroaeric levels corresponding to abscesses. (**b**) Infection—pleuropneumonia (mediastinal window): Extensive heterogeneous consolidation of lung tissue. In the damaged lung, there are areas of necrosis

dermatomyositis-polymyositis, it is also necessary to consider the coincidence with cancer, and in polymorbid patients, the manifestation of side effects of therapy, including possible pneumotoxicity.

7.13.4 Interstitial Lung Disease with Fluidothorax—What We Should Consider in Differential Diagnosis

1. Malignant mesothelioma: Very conspicuous bilateral asymmetric effusion, partially encapsulated in pleural pockets. Also, thickening of the pulmonary interstitium and fine, partially nodular, hyperdensities.
2. Infection—pleuropneumonia: Extensive heterogeneous consolidation of lung tissue. The proportion of pleural effusion is smaller compared to interstitial lung disease (Fig. 7.65a, b).
3. Paraneoplastic process in malignant disease: symmetric unilateral pleural effusion with an embolism in the right lower branch of the pulmonary artery, as a paraneoplastic manifestation (Fig. 7.66).

   These would also come into consideration in differential diagnostics: primary amyloidosis or pleural hyalinosis.

7.14 Smoking-Related Interstitial Lung Fibrosis

Martina Sterclova and Jana Votrubova

Male, 57 years old.
Patient coming in for examination of a cough.

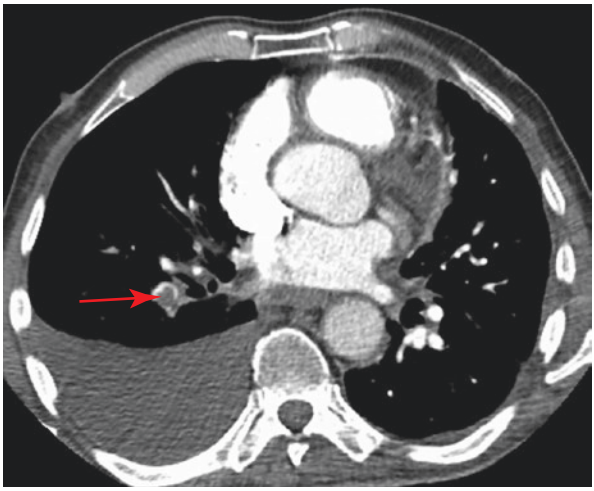


Fig. 7.66 Paraneoplastic process in malignant disease: symmetric unilateral pleural effusion with an embolism in the right lower branch of the pulmonary artery

Medical History

- Depression

Occupational History and Exposure

- Works as a forester, with a hobby of hunting
- Dogs at home
- Smoking history: never smoked

History of Present Complaint

- The patient began to cough about 4 months ago, expectorating yellow sputum. He did not have a temperature and denies exertional dyspnoea. He was examined by a respiratory physician in his local area, and a chest HRCT was performed. On the basis of an unclear finding, his case was consulted with our department, where the patient first underwent a bronchoscopy with bronchoalveolar lavage. For screening purposes, he also had autoantibody testing and the examination of specific IgGs. He attends an examination, during which he reports that he coughs significantly less.

Objective Finding

- Bilateral vesicular breathing and basal crepitations. No nail clubbing.

Examination

Lung Functional Tests

- FVC 3.97 L/97% (ref. v), VC_{max} 4.71 L/110% (ref. v), FEV_1 2.73 L/83% (ref. v), TLC 6.77 L/102% (ref. v), DL_{CO} 7.14 mmol/kPa/min/76% (ref. v).
- Ventilation practically in the standard range, with no restrictive ventilatory disorder. A slightly reduced transfer factor and an isolated change in the capillary component of the transfer factor.

Spiroergometry

- The load tolerance is slightly reduced. The circulatory response is adequate, however decreased cardiac output dynamics. The ventilatory response is mildly reduced, and there are signs of mechanical ventilation limitation. The respiratory response is normal. There are signs of physical deconditioning.

Radiology

- *Posteroanterior and lateral chest X-ray*: Bilateral strip-like shadows accentuated basally (Fig. 7.67a, b).
- *HRCT of the chest*: Combination of hyperinflation and fine GGO in the right upper and middle lobe, with reticulations and honeycombing basally (Fig. 7.68a–c).

Bronchoalveolar Lavage

- Haemorrhagic purulent secretions, with an estimated count of alveolar macrophages 20% and neutrophils 80%. Giant polyploid cells—grossly metaplastic.

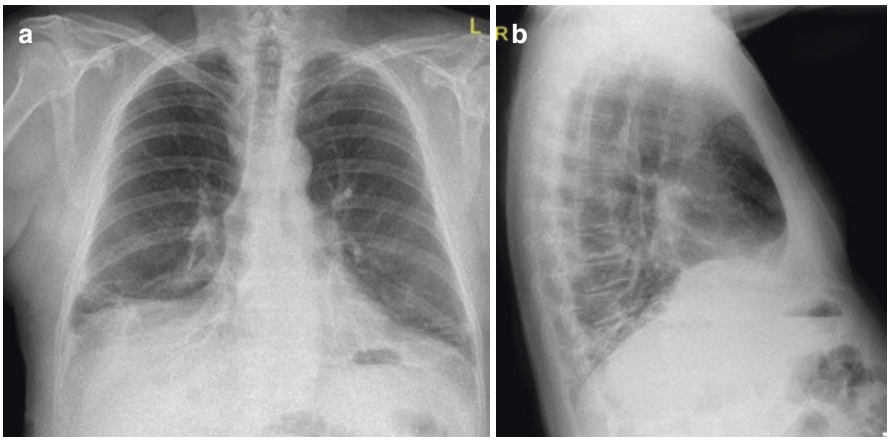


Fig. 7.67 (**a**) Posteroanterior chest X-ray: strip-like shadows accentuated basally. (**b**) Lateral chest X-ray: basally strip-like shadows

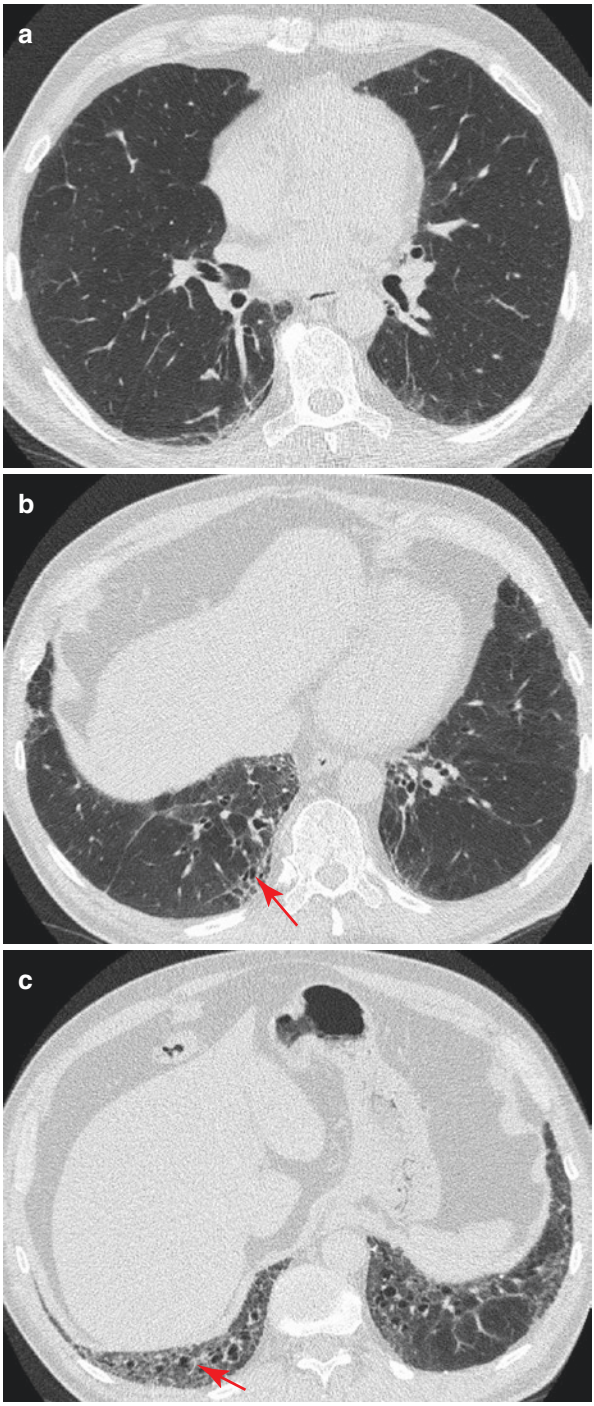


Fig. 7.68 (**a**) HRCT of the chest: hyperinflation with fine GGO in dorsal areas. (**b**) HRCT of the chest: reticulation, and signs of dorsobasal fibrosis of honeycombing. (**c**) HRCT of the chest: reticulation, and honeycombing in dorsal basal parts of the lungs

Autoantibody Screening

- ANA neg., ENA neg., anti-dsDNA neg., RF neg., ANCA neg. Specific IgGs are indicative of exposure to fungi (59 mg/L) and animal hair (94.7 mg/L).

7.14.1 Multidisciplinary Team and Differential Diagnosis

Patient with an ILD that is dominantly involving the lungs basally, with probable fibrosis and retraction. The upper lobes have an increased amount of air. It is most likely idiopathic pulmonary fibrosis; however, the bronchoalveolar lavage cell count does not correspond to this picture. A VATS surgical pulmonary biopsy with a typical resection of the right upper and lower lobe is recommended.

VATS and Histology

- In both samples, there is severe interstitial fibrosis, with a completely unpreserved pulmonary tissue architecture, and significant bronchiolisation. We can also find individual microscopic ossifications. There are highly advanced signs of a combination of desquamative interstitial pneumonia and smoking-related interstitial fibrosis (SRIF).

Additional History from the Patient

- Two years, he states he may have inhaled fumes from a slash pile burning in the woods, and cement dust (containing aluminium and iron compounds). He denies passive exposure to cigarette smoke.

7.14.2 Conclusion

- An ILD with histological signs of desquamative interstitial pneumonia and SRIF
- Fitness training is recommended, with no therapy

7.14.3 Smoking—Related Interstitial Fibrosis

The term SRIF first appeared in the research of Kazenstein et al. (2010), the authors used it to describe the histological image of interstitial changes in the lungs of patients who smoke or used to smoke. Changes in the pulmonary interstitium were captured in 60% of the examined samples, obtained by lobectomy in patients undergoing lung resection for bronchogenic carcinoma. The term SRIF refers to chronic

interstitial lung fibrosis, with a characteristic thickening of the alveolar septa based on collagen deposition and minimal participation of inflammation. Changes dominate subpleurally and are usually associated with centrilobular emphysema.

SRIF also has a radiological correlation and can be distinguished from both UIP and combined pulmonary fibrosis syndrome with emphysema. According to some research, SRIF is indicated by asymmetric/heterogeneous honeycombing, and by the presence of emphysema in close proximation to honeycombing, with the absence of honeycombing subpleurally. In addition, honeycombing in the upper pulmonary lobes is generally missing, and in the areas affected by honeycombing, there is no reticulation.

In the above-mentioned patient, SRIF was not histologically confirmed as related to the history of nicotinism, but to the exposure of wood burning fumes and inorganic dust. Very similar changes have been described in people who were exposed to dust, vapours, and gases during the World Trade Centre (WTC) disaster in 2001. This involved not only the rescuers but also those individuals who cleaned the debris or lived near the WTC. The connection of the potential negative effects of combustion fumes on the pulmonary parenchyma is also documented in the cases of soldiers, who were massively exposed during the disposal of waste in combustion pits during conflicts in the Middle East.

Note

Pulmonary damage resulting from exposure to inorganic inhaled antigens may not always have a typical radiological or histopathological image. The healing pattern in which the lung tissue responds to damage can be in line with the healing patterns seen in patients with idiopathic pulmonary pneumonia. On the other hand, the causal relationship between the exposure and the pulmonary disease mostly cannot be unambiguously proved or ruled out, and the possible impact of further therapy for a particular patient must be taken into account when determining the diagnosis.

7.14.4 Smoking-Related Interstitial Fibrosis—What We Should Consider in Differential Diagnosis

1. Hypersensitivity Pneumonitis: In chronic stages, fine GGO within fine markings of thickened septa and minor bronchiectasis (Fig. 7.69).
2. Fibrosing NSIP: Fine reticulations peripherally, with unaffected subpleural parts of the lungs (Fig. 7.70).
3. Idiopathic pulmonary fibrosis: Very conspicuous reticulations predominantly subpleurally and dorsobasally with pulmonary parenchyma distortions (Fig. 7.71a, b).

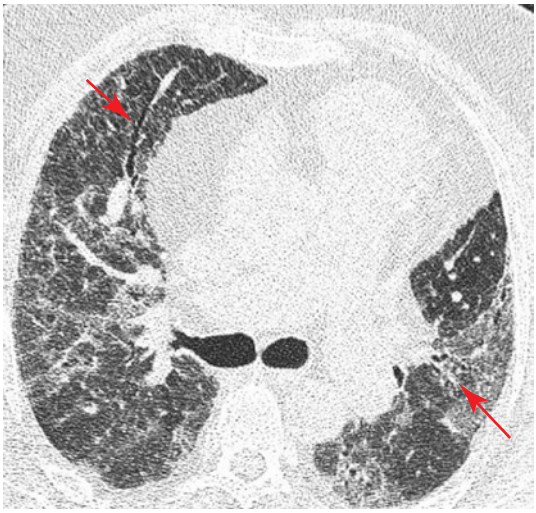


Fig. 7.69 Hypersensitivity Pneumonitis: fine GGO within thickened septa and minor bronchiectasis

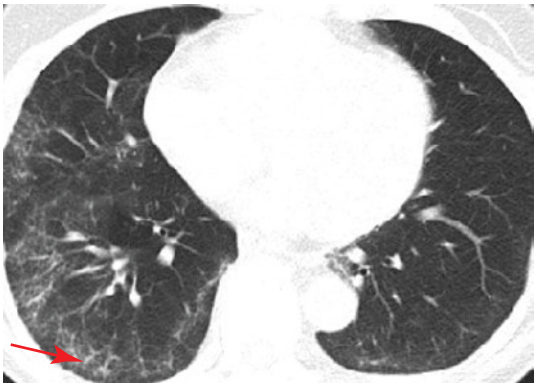


Fig. 7.70 Fibrosing NSIP: Fine reticulations peripherally

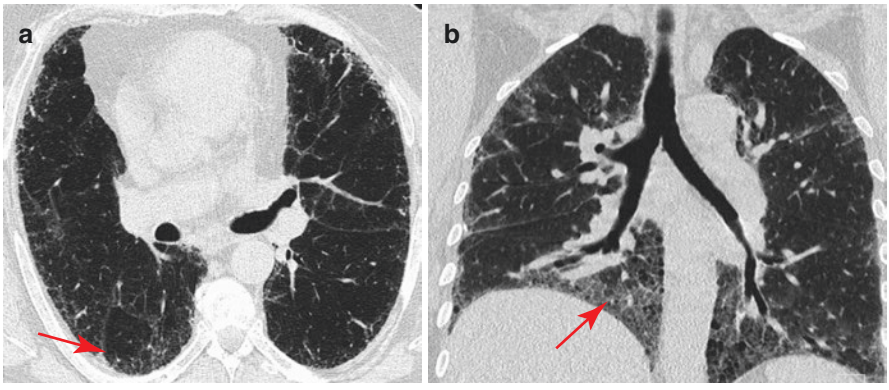


Fig. 7.71 (**a**) Idiopathic pulmonary fibrosis: reticulations predominantly subpleurally. (**b**) Idiopathic pulmonary fibrosis (coronal reconstruction): reticulations predominantly subpleurally and basally with pulmonary parenchyma distortions, traction bronchiectasis

7.15 Asbestosis

Filip Ctvrtlik and Vladimira Lostakova

Male, 74 years old.
Patient presenting with dyspnoea and a cough.

Medical History

- Type 2 Diabetes Mellitus—on oral anti-diabetic therapy, hyperlipoproteinemia, hypertension, IHD, implantation of cardiostimulator 2000, previous MI 8/2008, TIA 10/2009
- Smoking history: ex-smoker, smoked for 43 years up to 20 cigarettes a day until 1998

Occupational History and Exposure

- Currently retired. Previously worked for 16 years in the factory ETERNIT in Šumperk (Czech Republic)—dealing with the production of fibre cement in building and construction materials, with asbestos risk. He then worked within the agricultural cooperative.

History of Present Complaint

- The patient was sent for examination from the Department of Occupational Medicine in Olomouc (Czech Republic), where he has been observed since 2005, as part of asbestos risk monitoring for pleural hyalinosis and obstructive ventilatory disorder. He was examined at the Department of Respiratory Medicine in Olomouc for the first time in 12/2012 for progressive dyspnoea (now at minimal exertion) and a dry cough. There is no weight loss reported and he denies haemoptysis, chest pain, and palpitations.

Objective Finding

- Heart sounds are regular, lung percussion resonant, vesicular breathing with no epiphenomena. Lower extremities are without oedema.

Examination

Lung Functional Tests

- VC 3.39 L/72% (ref. v), FEV_1 2.41 L/70% (ref. v), TI% VC_{max} 71%, MEF25 45%, TLC 87%
- A slight decrease in VC at normal TLC, no obstruction, RV normal and increased airway resistance
- DL_{CO}sb: DL_{CO} 45%, K_{CO} 69%

- A moderate reduction in transfer factor and a mild reduction of transfer coefficient

Auxiliary and Laboratory Examinations

- Full blood count—anaemia, and no leucocytosis. Biochemistry, including CRP, is normal.
- Soluble Mesothelin-Related Peptide levels (SMRP): 1.82; 2.14.

Radiology

- *Posteroanterior and lateral chest X-ray*: Under the left clavicle is a pacemaker shadow. Lung lobes are expanded. Bilaterally, numerous reticulations are apparent. Vascular markings are accentuated, and there is widening of the cardiac shadow.
- *HRCT of the lungs*: The CT scans are dominated by bilateral, symmetric involvement of the pulmonary interstitium, with a predominance of the changes peripherally and basally. Irregular reticulations, and also traction bronchiolectasis, are evident in the periphery. Quite insignificant GGO are apparent. In the mediastinal window, the thickening of the parietal pleura (pleural plaques) with calcifications is highlighted. There is dorsobasal concurrent inconspicuous fluidothorax noted on the right (Fig. 7.72a–f).

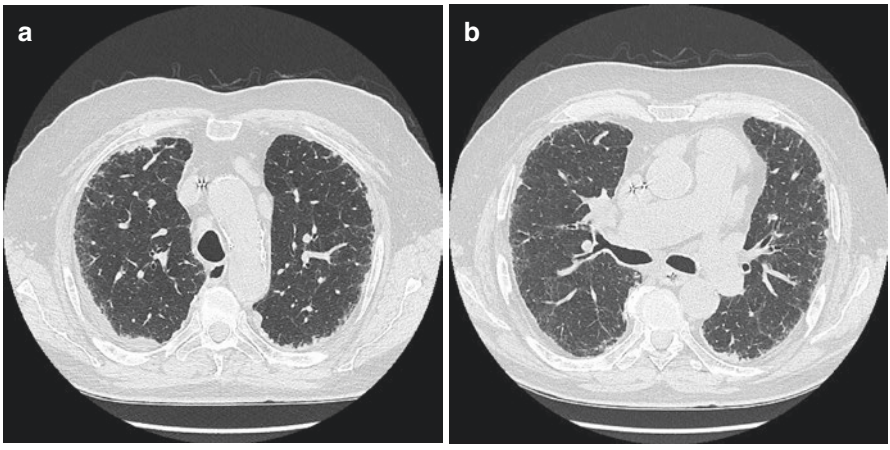


Fig. 7.72 (**a**) HRCT of the lung: irregular reticulations. (**b**) HRCT of the lung: symmetric subpleural reticulations. (**c**) HRCT of the lung: reticulation and patchy areas of GGO. (**d**) HRCT of the lung: reticulation, and also traction bronchiolectasis apparent in the periphery. Quite insignificant GGO is present. (**e**) HRCT of the lung (coronal reconstruction): reticulations, predominance of the changes peripherally and basally. (**f**) HRCT of the lung (mediastinal window): thickening of the parietal pleura (pleural plaques) with calcifications. On the right, a dorsobasal concurrent inconspicuous fluidothorax is noted

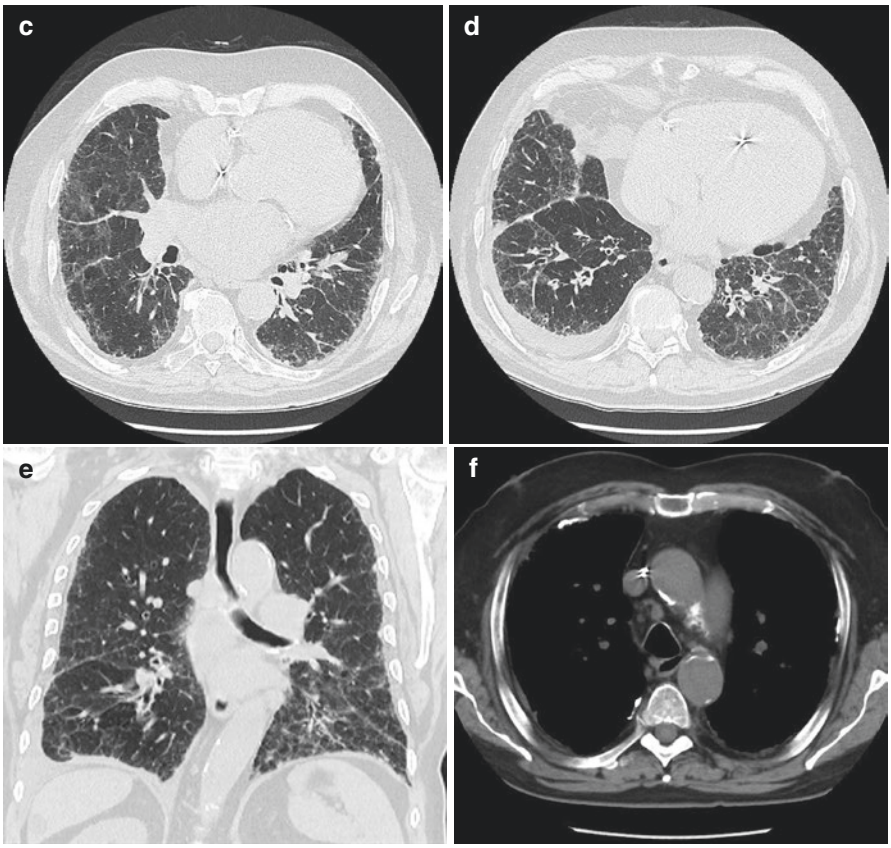


Fig. 7.72 (continued)

Bronchoscopy and Bronchoalveolar Lavage

- *BAL in 2016*: alveolar macrophages 87%, lymphocytes 4%, neutrophils 4%, eosinophils 5%. *Conclusion*: eosinophilic alveolitis, with borderline neutrophils.
- *TBB*: Not performed. A VATS pleural biopsy has been performed—see below.

7.15.1 Multidisciplinary Team and Differential Diagnosis

The findings clearly support the diagnosis of asbestosis.

7.15.2 Conclusion

The patient has been observed for a long time at the Occupational Health Medical Clinic of Olomouc Hospital, since 2005, for being at high risk of asbestosis, pleural hyalinosis, and obstructive pulmonary disease. In 2012, findings affecting the pulmonary interstitium were radiologically confirmed and assessed as asbestosis. Subsequently, the patient was monitored at the Department of Respiratory Medicine at University Hospital Olomouc. Radiologically, there has been a progression of the interstitial changes, including effusion, worsening of the symptoms and an elevation of SMRP. Due to the development of respiratory insufficiency in 2014, he was indicated for LTOT.

In April 2016, a VATS biopsy of the pleura was performed, and a lower right lobe deposit was histologically verified as malignant mesothelioma. He was treated with chemotherapy (cisplatin, carboplatin, followed by 6 cycles of CBDCA + Alimta chemotherapy). Since September 2016 the patient was only monitored, and was stable during the last check-up in January 2017, without any signs of recurrence of the disease.

Note

- Exposure to asbestos may lead to a benign pleural defect—pleural hyalinosis or may affect the pulmonary interstitium—asbestosis or even malignancy—mesothelioma and bronchogenic carcinoma.
- On the finding of fibrous changes (with the predominance in the periphery of the lung lobes) in patients with a positive history of working with asbestos, the thought of asbestosis is essential. In the differential diagnosis of the HRCT findings, UIP/IPF, drug-induced disorder and lung disorder in connective tissue disease have to be considered, as they may have the same image on HRCT.

7.15.3 Asbestosis—What We Should Consider in Differential Diagnosis

1. NSIP: In the peripheral parts of the lower lobes, there are regions of GGO, reticulations, and inconspicuous traction bronchiolectasis (Fig. 7.73).
2. UIP: Predominant changes are subpleurally and basally, where reticulations, traction bronchiolectasis, and honeycombing are apparent. UIP, unlike asbestosis, does not have pleural plaques (on the other hand, asbestosis may occur even without the presence of the plaques) (Fig. 7.74).
3. Connective tissue disease (scleroderma): The predominant changes are peripheral, where reticulations are apparent. There are only discreet ground glass opacities. Connective tissue affection can also be associated with other interstitial pneumonia, most commonly with NSIP (Fig. 7.75).
4. Drug-induced disorder (cyclophosphamide): For the diagnosis, pharmacological history is fundamental (Fig. 7.76).

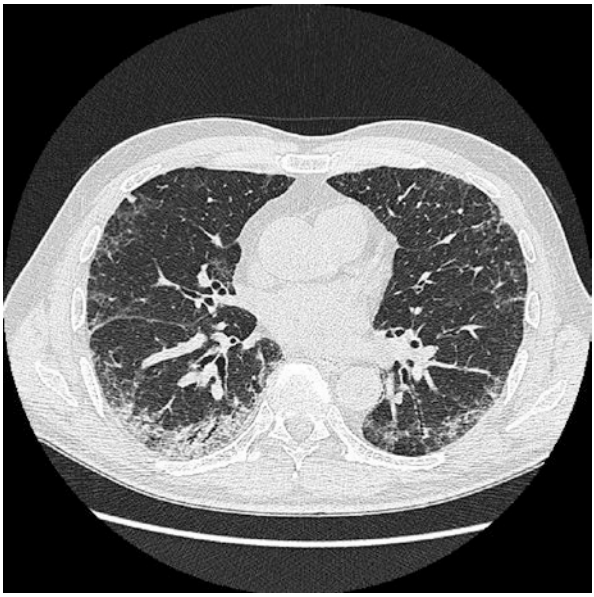


Fig. 7.73 NSIP: GGO and reticulations, inconspicuous traction bronchiolectasis

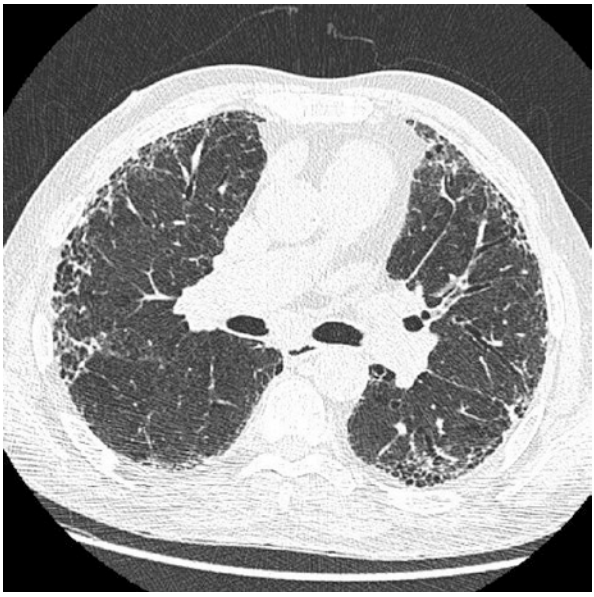


Fig. 7.74 UIP: reticulations, traction bronchiolectases, and honeycombing in periphery of the lungs

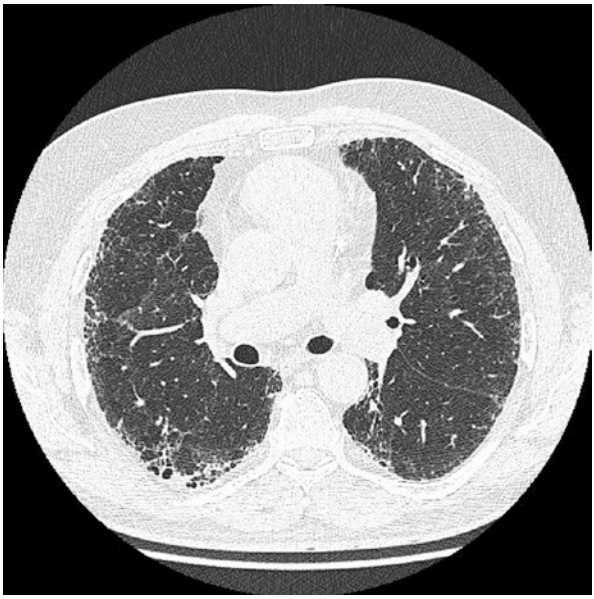


Fig. 7.75 Connective tissue disease (scleroderma): peripheral reticulations, only discreet ground glass opacities, traction bronchiolectasis

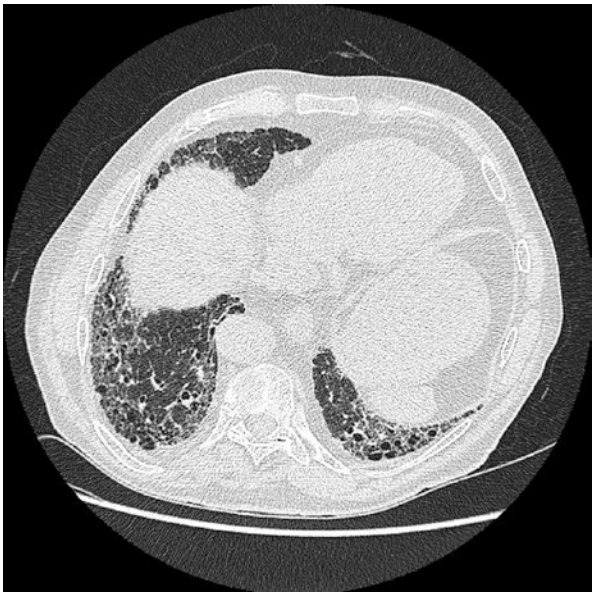


Fig. 7.76 Drug-induced disorder (cyclophosphamide): Predominance of changes is peripheral and basal, where there are findings of reticulations, traction bronchiolectasis, honeycombing, and a small amount of GGO are apparent

7.16 Pleuroparenchymal Fibroelastosis

Eva Kocova and Vladimir Bartos

Female, 74 years old.
Patient with dyspnoea and cough.

Medical History

- Hypothyroidism—in substitutional therapy, otherwise insignificant

Occupational History and Exposure

- Without high-risk environmental exposure or medication
- Smoking history: non-smoker

History of Present Complaint

- A sportswoman with a prolonged cough and progressive exertional dyspnoea, which became aggravated after an infection of the upper respiratory tract. The infection was being treated with antibiotics, which were completed half a year ago without effect. A chest X-ray was performed for persistent symptoms.

Objective Finding

- Vesicular breathing, basal crepitations, with substantial nail clubbing on the fingers and toes. Otherwise, other findings are normal.

Examination

Lung Functional Tests

- Normal ventilation parameters—no obstructive or restrictive ventilatory disorder
- FVC 2.32 L/88% (ref. v), FEV_1 2.03 L/93% (ref. v), Tiff. 80%, MEF50 83% (ref. v), RV 2.16 L/97% (ref. v), TLC 4.69 L/88% (ref. v), RV/TLC 46
- Moderately reduced transfer factor for CO, mild reduction of transfer coefficient (DL_{CO} 3.59/49% (ref. v), K_{CO} 0.95/68% (ref. v))

Radiology

- *Posteroanterior chest X-ray*: Numerous bilateral reticulations, thickened pleura apically, and apical bronchiectasis to the right (Fig. 7.77).
- *HRCT of the lungs*: Bilateral apical pleural thickening with conspicuous traction bronchiectasis, which stretches cranially from the hila. Subpleural reticulations and also traction bronchiectasis, are evident ventrally and basally. There is ventral honeycombing in the upper lobes, and dorsally in the lower lobes (Fig. 7.78a–d).

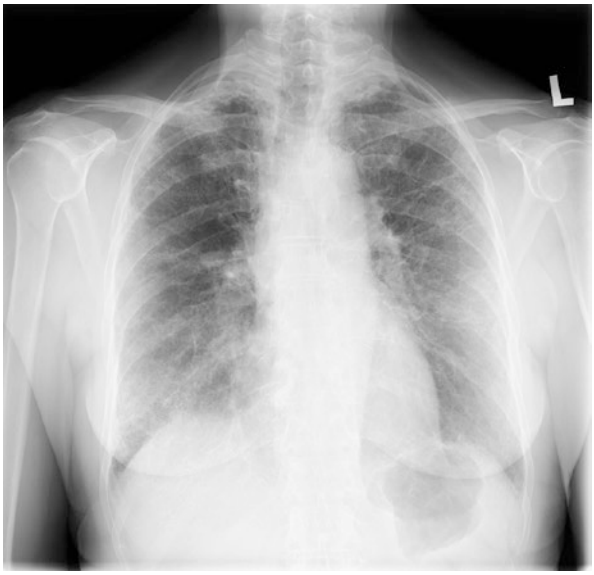


Fig. 7.77 Chest X-ray: lungs are expanded, bilateral numerous reticulations, thickened apical pleura, bronchiectasis in the right upper lobe

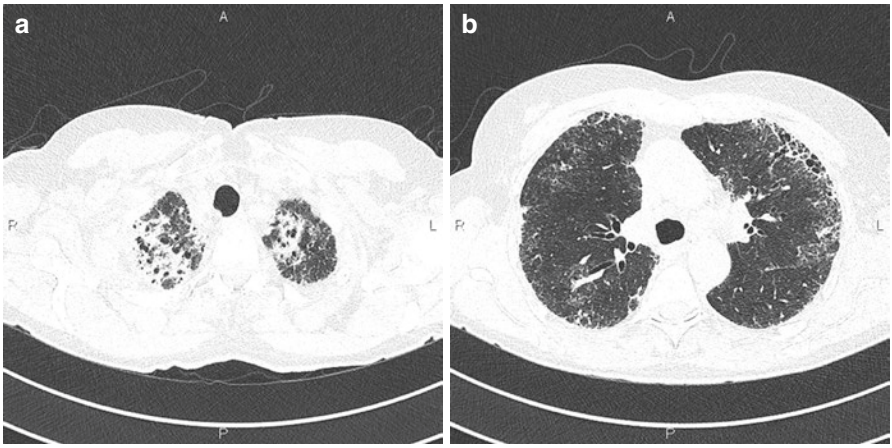


Fig. 7.78 (**a**) HRCT of the lungs: bilateral peribronchial multiple regions of consolidations, with a preserved air bronchogram. (**b**) HRCT of the lungs: bilateral reticulations, peribronchial multiple regions of GGO. (**c**) HRCT of the lungs: especially bilateral subpleural reticulations, and traction bronchiectasis. (**d**) HRCT of the lungs: bilateral subpleural reticulations, and traction bronchiectasis

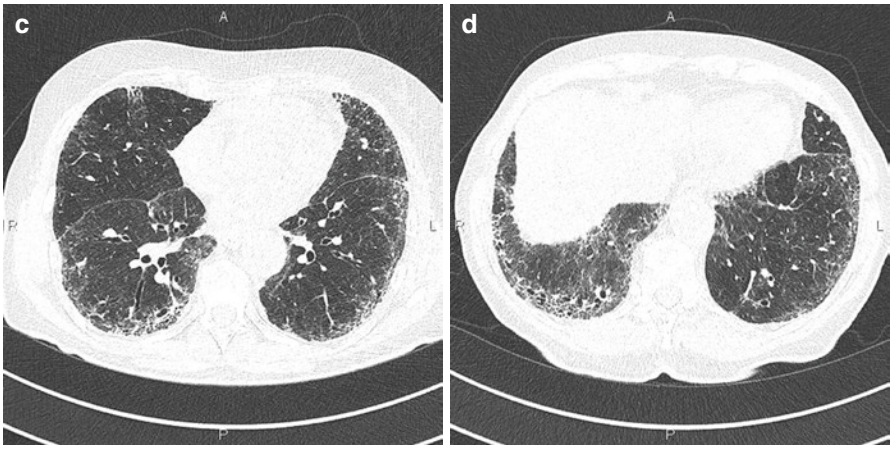


Fig. 7.78 (continued)

Laboratory Examination

- Normal blood count and biochemical parameters, without the evidence of SCTD, autoimmunity or immunodeficiency. The IGRA tests for TB are negative.

7.16.1 Multidisciplinary Team and Differential Diagnosis

A fibrosing ILD with significant fibrosis in the upper and lower lobes, honeycombing and traction bronchiectasis. CT findings could correspond with UIP in combination with PPFE for conspicuous fibrous changes and apical pleural thickening.

The conclusion of the MDT: MDT indicates a bronchoscopic examination with lung cryobiopsy and bronchoalveolar lavage to elucidate the findings (although some authors do not recommend histological verification for suspected PPFE for risk of complications, especially persistent pneumothorax).

Bronchoscopically and macroscopically the findings are normal. In the bronchoalveolar fluid, there is no evidence of infection (or specific infections), and no malignant cells or foreign bodies (asbestos fibres, etc.) have been detected. The cytological differential count is without lymphocytosis (4% lymphocytes), however, indicated a slight neutrophilia and eosinophilia (10% neutrophils, 4% eosinophils).

Lung cryobiopsy: Identified heterogeneity of the findings in the samples taken. The first sample revealed significant pulmonary fibrosis with fibroblastic foci, and without complete honeycombing. The second sample manifested the typical image of PPFE, including staining of elastic fibres.

7.16.2 Conclusion

According to HRCT signs, cryobiopsy and BAL findings, the diagnosis was identified as PPFE with a UIP pattern of fibrosis.

7.16.3 Pleuroparenchymal Fibroelastosis—What We Should Consider in Differential Diagnosis

1. Hypersensitivity Pneumonitis: In chronic HP, there is a more pronounced thickening of the peribronchovascular interstitium, with regions of normal pulmonary parenchyma—a typical "head cheese" sign (Fig. 7.79).
2. Stage IV sarcoidosis: Apical fibrosis, with perilymphatic nodules (Fig. 7.80).
3. Usual interstitial pneumonia in systemic connective tissue disease: Signs of UIP patterns, in a patient with a history of SCTD (Fig. 7.81).
4. Specific infection: typical patterns of the tree-in-bud nature, consolidations apically (Fig. 7.82).
5. Conditions after lung injury with contusion and scarring: possible occurrence of pleural fibrosis with traction changes (with known traumatic history) (Fig. 7.83).

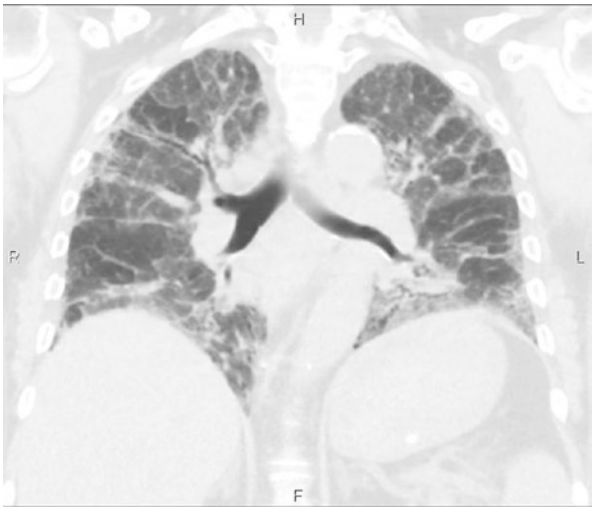


Fig. 7.79 HRCT of the lung (coronal reconstruction): Hypersensitivity Pneumonitis: thickening of the peribronchovascular interstitium, with regions of normal pulmonary parenchyma—a typical "head cheese" sign

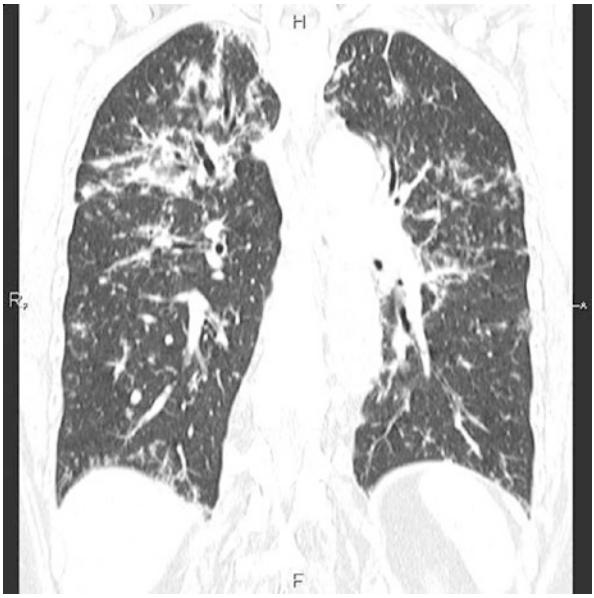


Fig. 7.80 Stage IV sarcoidosis: Apical fibrosis, with multiple perilymphatic nodules

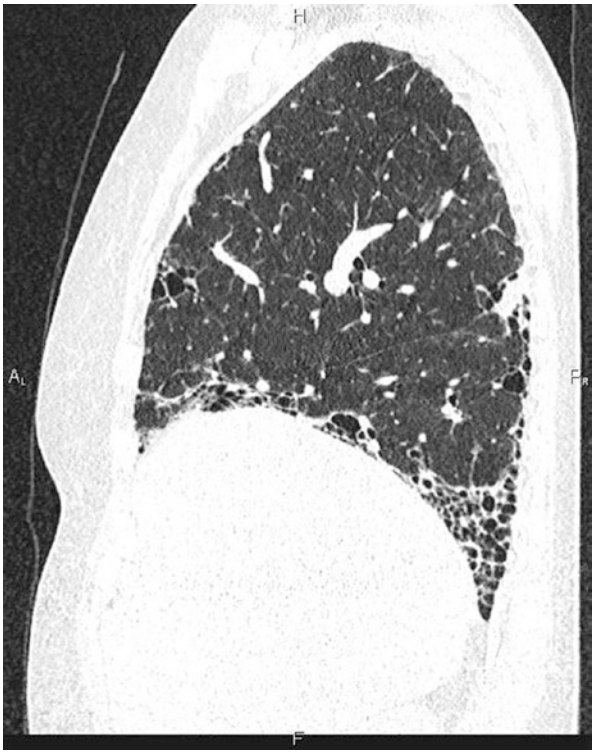


Fig. 7.81 Usual interstitial pneumonia in systemic connective tissue disease (HRCT sagital reconstruction): UIP patterns

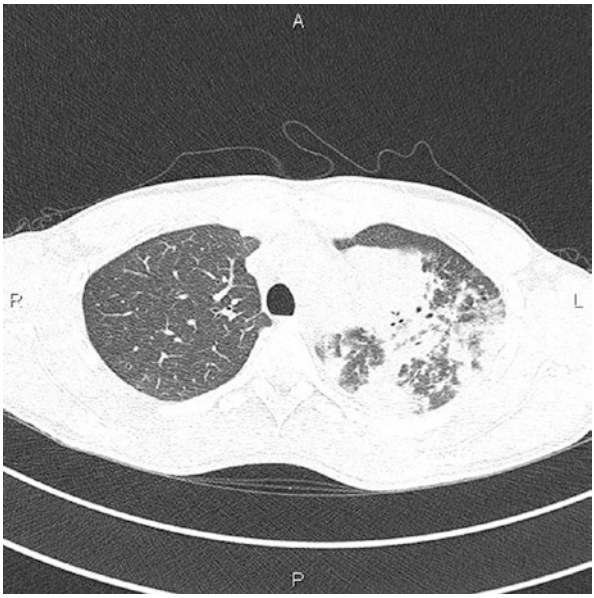


Fig. 7.82 Tuberculosis: consolidations, tree-in-bud patterns on the left side

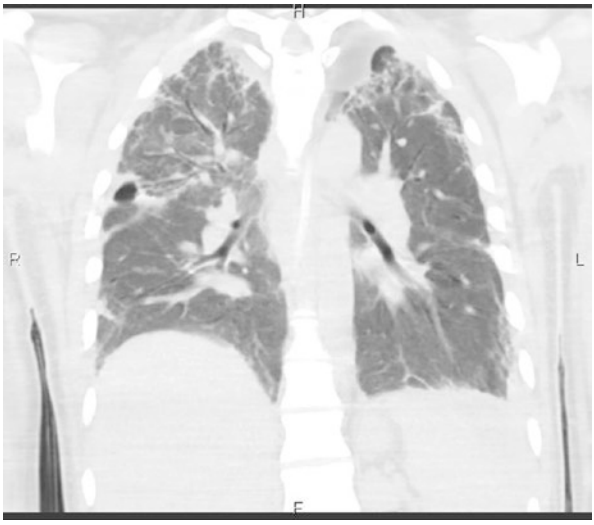


Fig. 7.83 HRCT of the lung: contusion, pneumatocele on the right side

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Nodulations

8

Eva Kocova, Vladimir Bartos, Filip Ctvrtlik, Vladimíra Lostakova, Monika Zurkova, Martina Sterclova, and Jana Votrubova

8.1 Sarcoidosis I

Eva Kocova and Vladimir Bartos

Female, 48 years old.

Examined for a chronic dry cough, progressive exertional dyspnoea over the last year, exhaustion, weakness and fatigue.

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_8

Medical History

- Local lichen planus—dermatological treatment
- Otherwise healthy

Occupational History and Exposure

- Works in a clean environment without significant exposure to organic or inorganic dust
- Smoking history: non-smoker

History of Present Complaint

- About for a year, she observes progressive dyspnoea and a dry, tickly cough. Over the last 2 months, her symptoms have aggravated, with a feeling of heavy breathing and chest tightness. Additionally, occasional hoarseness and a persistent feeling of fatigue, weakness, and exhaustion.

Objective Finding

- Normal patent airways, vesicular breathing, without secondary phenomena. A discreet skin finding of lichen planus (histologically verified).

Examination

Lung Functional Tests

- FVC 1.83 L/69% (ref. v), FEV_1 1.25 L/56% (ref. v), Tiff. 68%, maximal expiratory flow (MEF50) 1.68/32% (ref. v), RV 2.71 L/176% (ref. v), TLC 4.55 L/106% (ref. v), RV/TLC 60%, DL_{CO} 4.85/65% (ref. v).
- A moderate obstructive ventilatory disease with a mild limitation of vital capacity with pulmonary hyperinflation. No restrictive ventilatory disorder. Slightly reduced lung diffusion for CO.

Radiology

- *Posteroanterior chest X-ray*: The finding is adequate with the age and constitution of the patient.
- *HRCT of the lungs*: Mediastinal and bilateral hilar lymphadenopathy. Nodes are without necrosis and calcifications. In the pulmonary parenchyma, there is no clear pathological finding (Fig. 8.1).

Bronchoscopy, Bronchoalveolar Lavage and EBB and TBB

- Normal endobronchial findings, except for a slightly dull carina and increased mucus secretion from the mucous membranes. A series of endobronchial biopsies (EBB) of the mucous membranes, TBB and BAL have been performed.

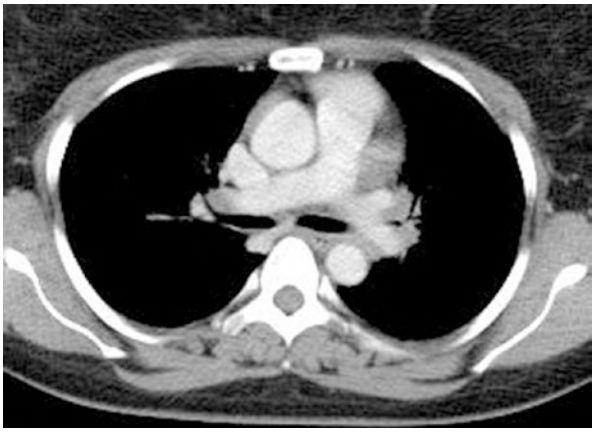

Fig. 8.1 HRCT of the lungs (mediastinal window): bilateral symmetrical hilar lymphadenopathy

- EBB + TBB: Signs of an inflammatory disorder of the bronchial mucosa with a granulomatous component. The pulmonary parenchyma patterns also have evidence of multiple lung diseases due to structures of multiple specific granulomas formed by epithelioid and polynuclear cells. The granulomas are not necrotizing, and thus a differential diagnostic, especially sarcoidosis, is considered. Specific staining does not indicate infectious agents.
- BAL: Multicellular, increased lymphocyte count (47%), CD4+ lymphocyte predominance (78%), CD8+ lymphocytes 18%, i.e. immunoregulation index 4.3, cell clonality not proved, granulocytes 1%, macrophages 51%, and malignant cells not detected. Microbiology culture and PCR do not identify infection or specific infection (without evidence of tuberculosis mycobacteria or atypical mycobacteria).

Auxiliary and Laboratory Examinations

- Laboratory: Blood count and biochemical examinations are normal, inflammatory markers are low, normocalcaemia and normocalciuria. Elevation of serum angiotensin-converting enzyme (SACE) and significant elevation of serum receptor for interleukin 2 (IL-2) have been identified. No autoantibodies or SCTD, no vasculitis, no cellular or antibody immunodeficiency have been found. The haematological examination did not illustrate haematological disease/malignancy, ENT and eye examination were physiological, and cardiological examinations including an echocardiography were of normal findings.
- Serological and cultural examination for infectious granulomatous processes is negative (HIV, syphilis, tularaemia, toxoplasmosis, toxocarosis, brucellosis, tuberculosis (TB), atypical mycobacteriosis, etc.).

8.1.1 Multidisciplinary Team and Differential Diagnosis

Evidence of symmetric lymphadenopathy, with TBB and EBB signs illustrating granulomatous inflammation without necrosis, and the BAL is compatible with

sarcoidosis. There is also unconfirmed infectious aetiology of a granulomatous process (HIV, syphilis, tularaemia, toxoplasmosis, toxocarosis, etc.), including a specific infection (TB, atypical mycobacteriosis). The patient has no risk factors for a drug-induced disorder or pneumoconiosis. SCTD or vasculitis has not been identified.

The diagnosis is determined as stage one intrathoracic sarcoidosis and obstructive sarcoid bronchitis. According to the patient's symptoms and declining pulmonary functions, oral corticosteroid therapy was initiated as per the protocol for sarcoidosis—inhaled corticosteroid therapy and bronchodilators for sarcoid bronchitis. However, despite therapy, there was an intermittent gradual progression of the pulmonary disease, with a decrease in pulmonary function. Therefore, the patient examined repeatedly over the course of 6 years (including BAL, serology, and histology). The further aetiological reasoning for the symptoms, other than sarcoidosis, has not been found. Gradually, the patient was treated with a combination of corticosteroids and additionally methotrexate, antimalarials, azathioprine, and even pulse therapy with methylprednisolone, with only partial effect. Then the patient developed steroid resistance.

8.1.2 Conclusion

The findings are compatible with the diagnosis of chronic, progressive, active, steroid-resistant sarcoidosis. Over time, the pulmonary disorder progressed on HRCT (bilateral parahilar consolidation, with multiple perilymphatic nodules), and there was a decrease in pulmonary function. There are also manifestations of extrathoracic sarcoidosis—with multiple splenic lesions and retroperitoneal lymphadenopathy.

Due to the progression, the patient was re-examined by a physician who authorised the initiation of biological therapy with infliximab (co-administered with long-term corticosteroid therapy and methotrexate), which initially had a beneficial effect. According to a follow-up PET/CT scan, there was a regression in the size of the pulmonary consolidations, retroperitoneal lymphadenopathy, and splenic lesions. However, an allergic reaction developed towards the biological therapy, leading to suboptimal compliance of the patient. The treatment was therefore terminated with an early relapse of the disease (Fig. 8.2a–c).

8.1.3 Pulmonary Sarcoidosis

Pulmonary sarcoidosis is a disease of unknown aetiology. However, with the use of imaging methods, the stages of the disease can be distinguished. The first stage of the disease remains only within the mediastinal and hilar nodes, without involvement of the pulmonary parenchyma. This is the fundamental stage at which a pivotal clinical and histological differentiation from lymphoma is identified.

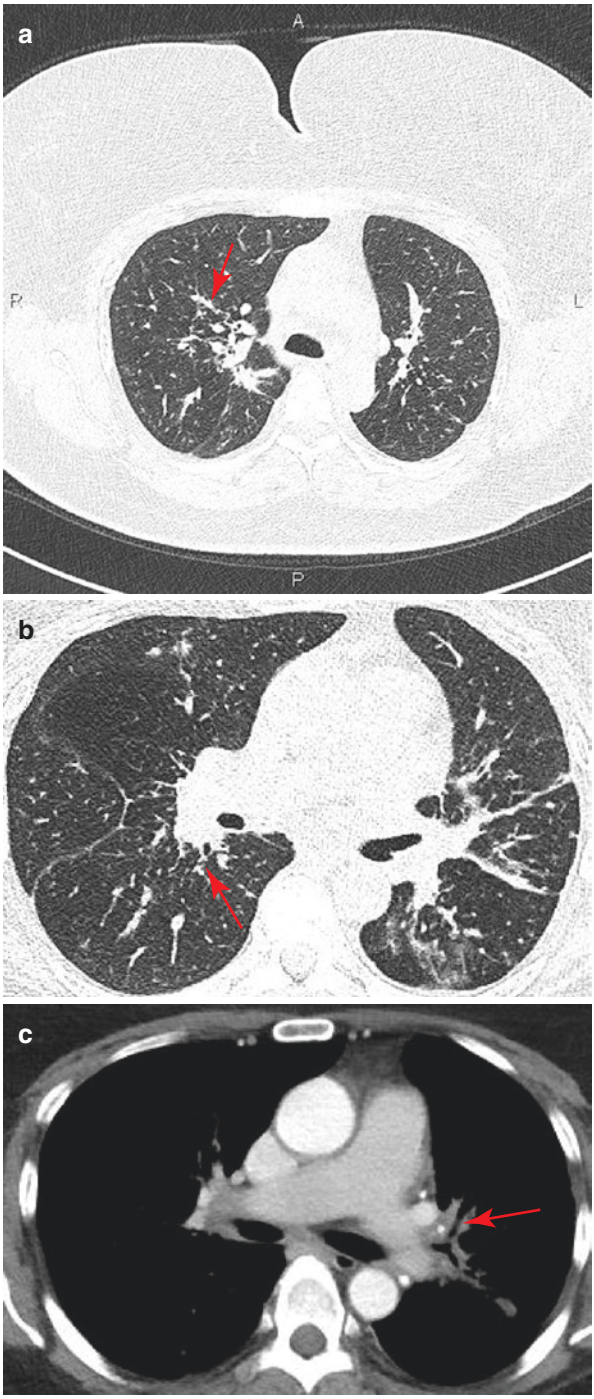

Fig. 8.2 (**a**) A repeat HRCT of the lungs, 2 years after diagnosis of sarcoidosis: new multiple small nodules in the perilymphatic distribution. (**b**) HRCT of the lungs, 4 years after diagnosis of sarcoidosis: multiple nodules in perilymphatic distribution. (**c**) CT of the lungs (mediastinal window): hilar lymphadenopathy, lymph nodes with calcifications

In the second stage, the lung parenchyma is impaired with small perilymphatic nodularities, typically distributed centrally and cranially. By the third stage, the pulmonary parenchyma involvement is already dominating. Small nodules may merge in conglomerates with nodularities on the periphery of the consolidations (galaxy sign).

During the fourth, terminal stage, there is pulmonary architecture distortion with scarring and fibrosis of the parenchyma, and traction of the hila in the cranial direction. In this stage, there are typical features of shell-like calcified mediastinal nodes.

Note

- Sarcoidosis is manifested in the first stage as mediastinal and symmetric hilar lymphadenopathy without the involvement of the pulmonary parenchyma.
- Radiologically, it is not possible to distinguish mediastinal sarcoidosis from lymphoma with certainty.
- In the subsequent stages of sarcoidosis, the small-nodular involvement of the pulmonary parenchyma is typical in a perilymphatic distribution, centrally and cranially. At this stage, differentiation of the perilymphatic distribution is fundamental, which is typical for sarcoidosis, but nevertheless non-pathognomic.

8.1.4 Sarcoidosis—What We Should Consider in Differential Diagnosis

8.1.4.1 Differential Diagnosis of Isolated Mediastinal Lymphadenopathy

1. Mediastinal lymphoma: If typical shell-like calcifications are not present, a lymphoma cannot be distinguished reliably radiologically from mediastinal node sarcoidosis (Fig. 8.3).
2. Central lung tumour: Stenosis of vascular structures, infiltration of mediastinal structures, and mostly asymmetric involvement of the mediastinum (Fig. 8.4).

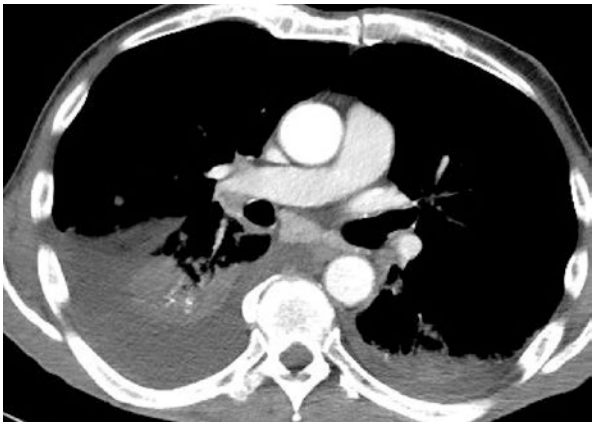

Fig. 8.3 Mediastinal lymphoma: mediastinal lymphadenopathy, fluidothorax bilaterally

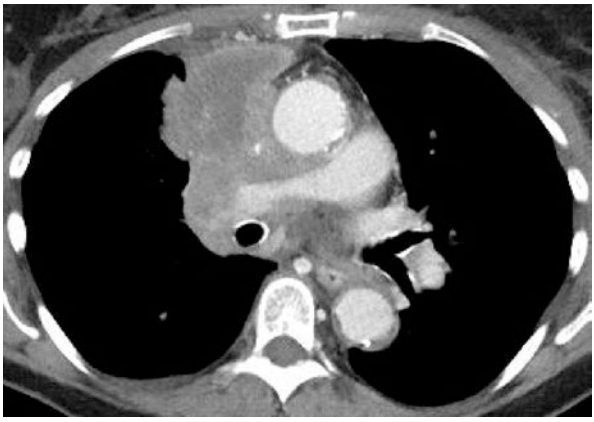

Fig. 8.4 Central lung tumour: Stenosis of vascular structures, infiltration of mediastinal structures

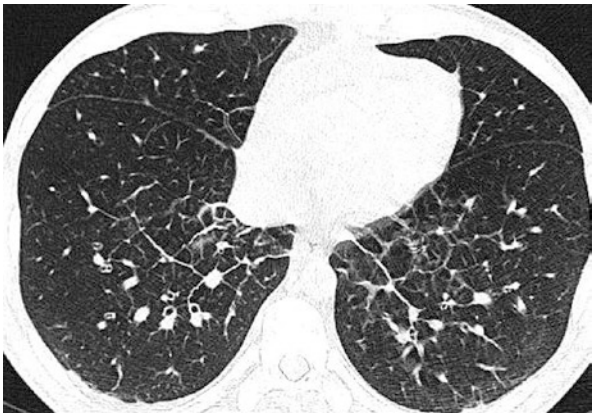

Fig. 8.5 Carcinomatous lymphangiopathy: septal thickening with nodules

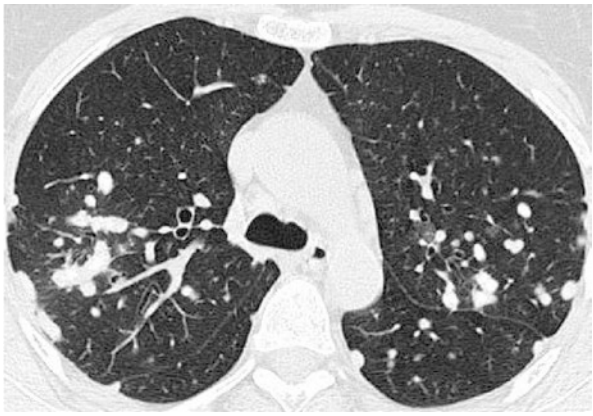

Fig. 8.6 Pneumoconiosis: multiple nodules in perilymphatic distribution

8.1.4.2 Differential Diagnosis of Lymphadenopathy and Perilymphatic Nodules

3. Carcinomatous lymphangiopathy: Oncological history (Fig. 8.5).
4. Pneumoconiosis: A history of exposure (Fig. 8.6).

8.2 Sarcoidosis II

Filip Ctvrtlik, Vladimira Lostakova, and Monika Zurkova

Male, 30 years old.

The patient is presenting with symptoms of dyspnoea and a productive cough of white sputum, concurrently with fading red efflorescences on the lower legs.

Medical History

- Treated for depression
- Allergy to penicillin

Occupational History and Exposure

- Works in archaeological research
- Smoking history: non-smoker

History of Present Complaint

- A 4 month lasting cough, with expectoration of whitish sputum, dyspnoea, and fading red efflorescences on the lower legs.

Objective Finding

- Vesicular breathing, without secondary phenomena.

Examination

Lung Functional Tests

- VC 4.20 L/88% (ref. v), FEV_1 2.97 L/80% (ref. v), FEV_1/VC 71% (ref. v), FEF75 41% (ref. v), TLC 93% (ref. v).
- DL_{CO}sb: DL_{CO} 93% (ref. v), DL_{CO}/V_A 113% (ref. v).
- Ventilation within the standard limits including RV. Due to TLC and respiratory tract resistances, there are signs of peripheral obstruction. Transfer factor and transfer coefficient are normal.

Auxiliary and Laboratory Examination

- Montoux Test (Mx II) 0 mm, QuantiFERON-TB negative, serum level of angiotensin-converting enzyme (SACE) 68.3, neopterin 2.68, IRI 1.3.

Radiology

- *Posteroanterior and lateral chest X-ray*: Symmetrical reticulonodulations in both lobes, with predominance in the mid-zones. Simultaneously, a slight enlargement of the pulmonary hilum bilaterally (Fig. 8.7).

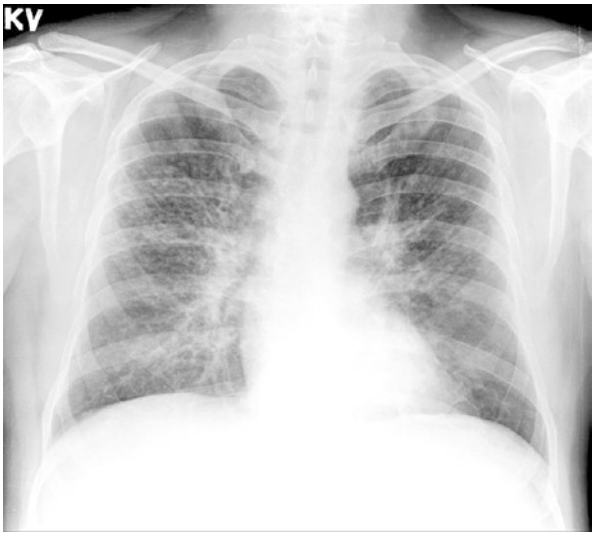

Fig. 8.7 Posteroanterior chest X-ray: symmetrical nodulations in both lobes; a slight enlargement of the pulmonary hilum bilaterally

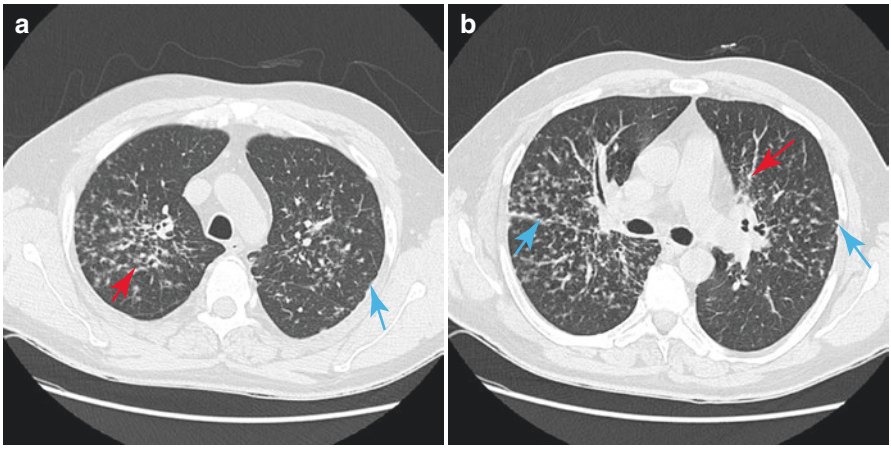

Fig. 8.8 (**a**) HRCT of the lungs: nodulations peribronchovascularly. (**b**) HRCT of the lungs: nodulations peribronchovascularly and on the pleura. (**c**) HRCT of the lungs: nodulations peribronchovascularly and on the fissure. (**d**) HRCT of the lungs (coronal reconstruction): nodules on the interlobar fissure. (**e**, **f**) HRCT of the lungs (sagittal reconstruction): nodulations on interlobar fissure

- *HRCT of the lungs*: Predominant peribronchovascular and parahilar nodules, and further on the pleura, especially on the interlobar fissure (beaded appearance). They are less apparent on interlobular septa and centrilobularly. The involvement of the upper and middle lung fields prevails, and within the mediastinum, including the hilum. Lymphadenopathy is not apparent (Fig. 8.8a–f).

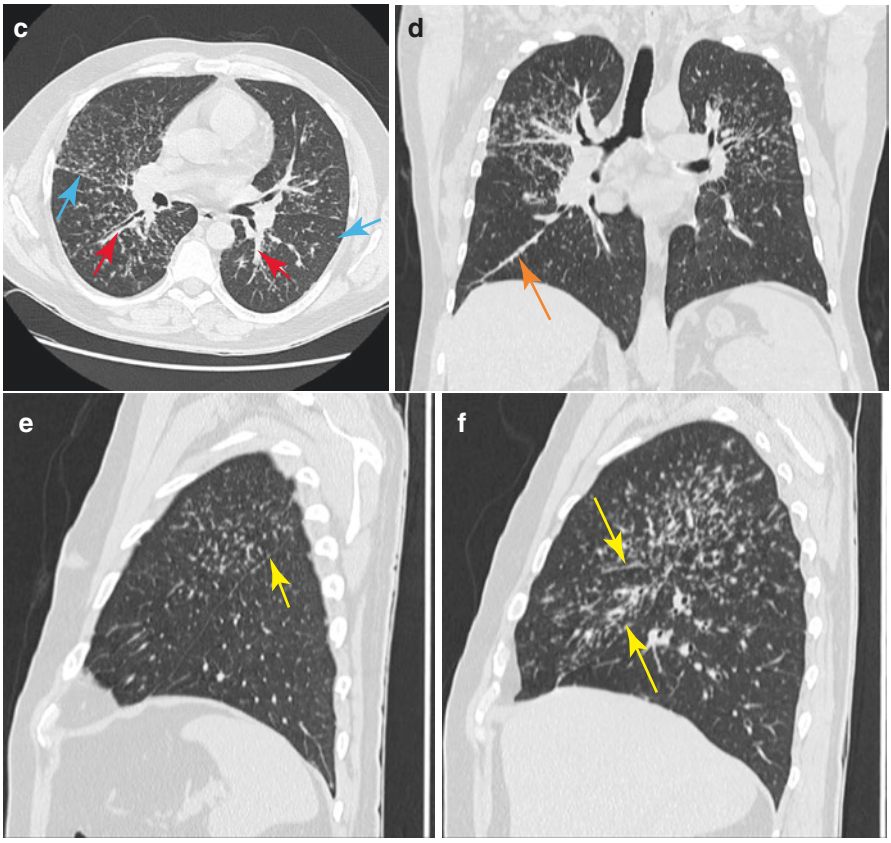

Fig. 8.8 (continued)

Bronchoscopy, Bronchoalveolar Lavage and TBB

- BAL: Lymphocytic (22%) and neutrophilic (8%) alveolitis, borderline eosinophils (2%), macrophages (68%), and suspected epithelioid cells.
- TBB: Fragments of the bronchial epithelium and part of the pulmonary parenchyma are found. The interalveolar septa are smooth, blood congested, without thickening, and a small deposit of fibrosis with an anthracotic pigment at the edge. Epithelioid granulomas are not present.

8.2.1 Multidisciplinary Team and Differential Diagnosis

With the available examinations, the aetiology of the disseminated lung disease was not confirmed. The BAL fluid cytology revealed a mixed alveolitis image. Histologically the TBB is ambiguous, IRI is low, and the biomarkers for sarcoidosis are negative. To support a diagnosis, the patient was indicated for a VATS biopsy,

which was performed without complications. Histologically, sarcoid granuloma was confirmed, and due to the extent of changes and clinical symptoms, corticosteroid therapy was initiated.

8.2.2 Conclusion

A combination of radiological findings, clinical presentation, and histopathological examinations corresponds to a diagnosis of sarcoidosis. Corticosteroid therapy is indicated due to the extent of changes and clinical symptoms.

Note

- The findings of nodules on the interlobar fissures (beading of the interlobar fissures), located centrally and peribronchovascularly, raises the suspicion of sarcoidosis.

8.2.3 Sarcoidosis—What We Should Consider in Differential Diagnosis

1. Silicosis: HRCT—When compared with sarcoidosis, in silicosis nodules are mainly centrilobular. Pathology is symmetrical and predominates in the upper and middle parts of the lungs. In the mediastinum, there are enlarged lymph nodes, often with shell-like calcifications. Diagnosis is supported by an occupational history that reports exposure to silica dust (Fig. 8.9a, b).
2. Coalworker's pneumoconiosis: HRCT findings are similar to silicosis. In the history, there is an occupational exposure (working in a mine) (Fig. 8.10).

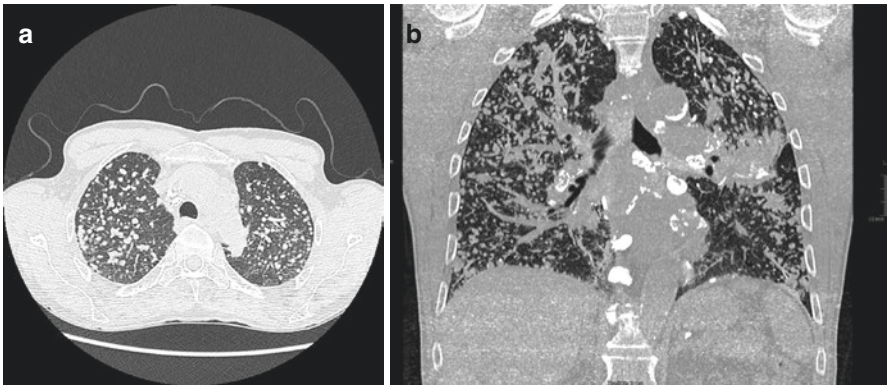

Fig. 8.9 (**a**) Silicosis: nodules are mainly centrilobular. (**b**) Silicosis: HRCT nodules are mainly centrilobular. Pathology is symmetrical and predominates in the upper and middle parts of the lungs. In the mediastinum, there are enlarged lymph nodes, often with shell-like calcifications

3. Carcinomatous lymphangiopathy: On HRCT, there is a predominant thickening of the interlobular septa, often unilaterally. Nodules are not a dominant morph. Patients with carcinomatous lymphangiopathy already have a known tumour or secondary CT findings that favour a malignant aetiology (asymmetrically enlarged lymph nodes in the mediastinum, bone metastases, liver metastases or adrenal glands) (Fig. 8.11).

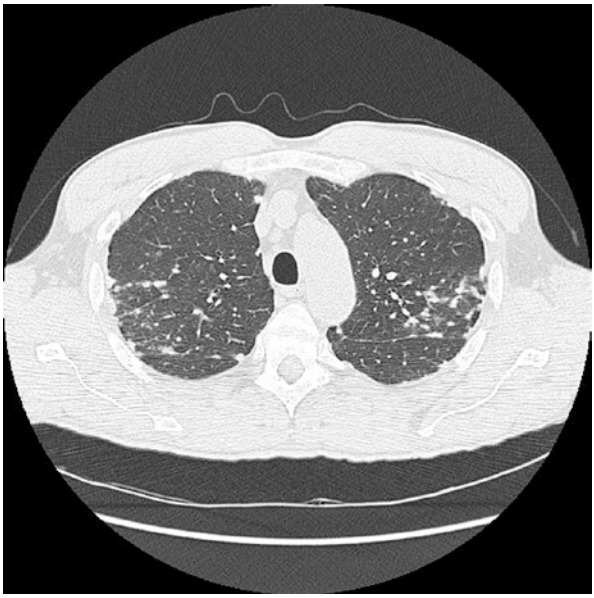

Fig. 8.10 Coalworker's pneumoconiosis: perilymphatic nodules

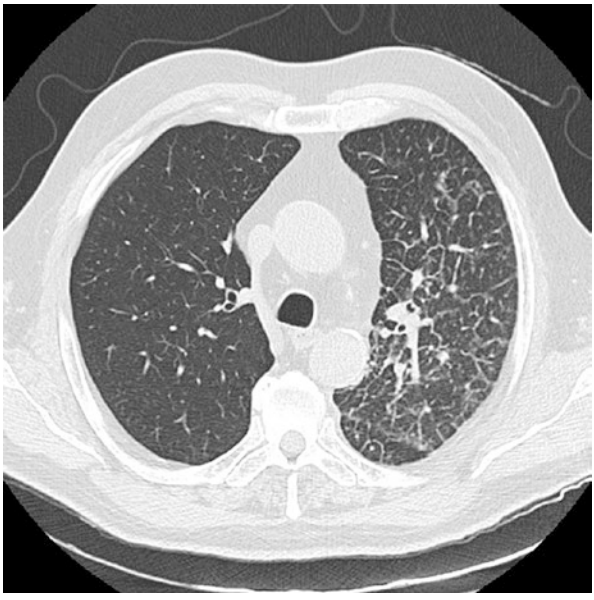

Fig. 8.11 Carcinomatous lymphangiopathy: thickening of interlobular septa with small nodulations

8.3 Miliary Tuberculosis

Filip Ctvrtlik, Vladimira Lostakova, and Monika Zurkova

Male, 90 years old.

The patient is attending for an examination for suspected pneumonia of interstitial lung disease nature.

Medical History

- Type 2 diabetes mellitus, on oral anti-diabetic therapy
- Suffered a stroke three times in the past
- Hypacusis
- Smoking history: non-smoker

Occupational History and Exposure

- Pensioner, formerly professional driver, no exposure

History of Present Complaint

- Transferred from the Emergency Department after 2 weeks of dyspnoea, chest pain, and elevated body temperatures. No cough or haemoptysis. Over the last 3 months he has lost about 10 kg, and at the same time complains of night sweats.

Objective Finding

- Regular heart rhythm, heart sounds normal. Lungs: vesicular breathing, basal crepitations, more to the left.

Examination

Lung Functional Tests

- VC 2.32 L/75% (ref. v), FEV_1 1.45 L/68% (ref. v), TI% VC_{max} 63% (ref. v), a mild obstructive ventilatory disorder with slightly reduced VC, RV, and TLC. Airway resistance is normal.
- DL_{CO} 24% (ref. v), K_{CO} 40% (ref. v), heavily reduced transfer factor, transfer coefficient moderately reduced

Auxiliary and Laboratory Examinations

- Full blood count indicates anaemia, and no leucocytosis. There is an elevation of CRP 37.0 mg/L, and an elevation of urea, creatinine, uric acid, and liver tests. A urine test is negative. Mantoux test (Mx II) is negative. IGRA (QFT) test is positive.

Radiology

- *Posteroanterior and lateral chest X-ray*: Diffuse small nodules apparent in both lobes (Fig. 8.12).
- *HRCT of the lungs*: Multiple diffuse, evenly distributed small, uniform and sharply bounded nodules (Fig. 8.13a–d).

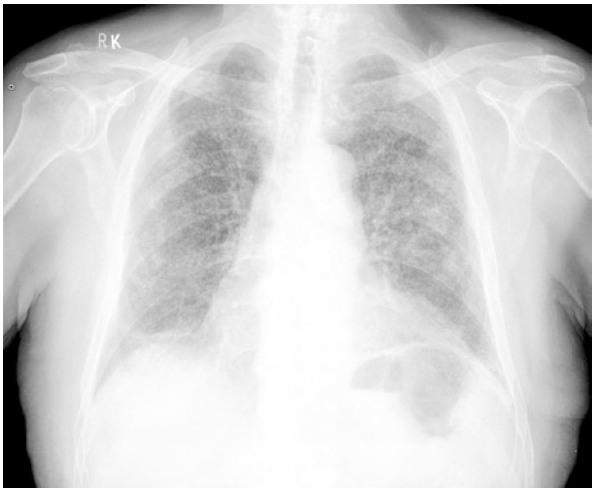

Fig. 8.12 Posteroanterior chest X-ray: diffuse, multiple, small nodules

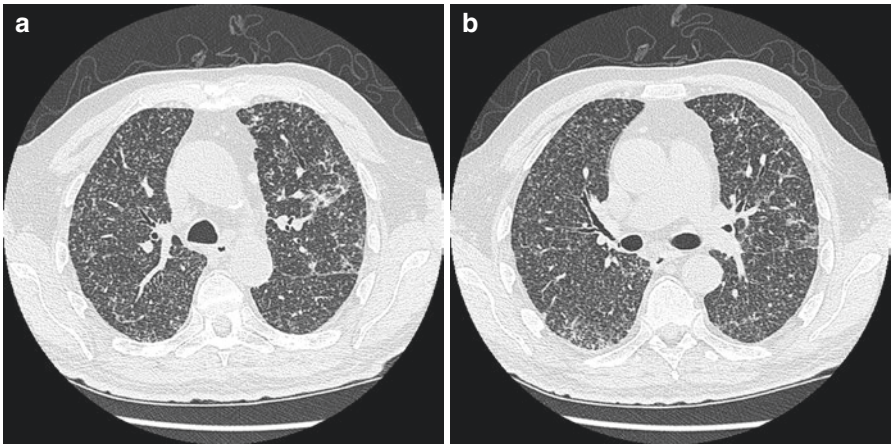

Fig. 8.13 (**a**) HRCT of the lungs: diffuse, multiple, uniform, and small sharply bounded nodules. (**b**) HRCT of the lungs: diffuse, multiple, uniform nodules in random distribution. (**c**) HRCT of the lungs: diffuse, multiple, uniform nodules. (**d**) HRCT of the lungs (coronal reconstruction): diffuse, multiple, uniform, small sharply bounded nodules in whole lungs

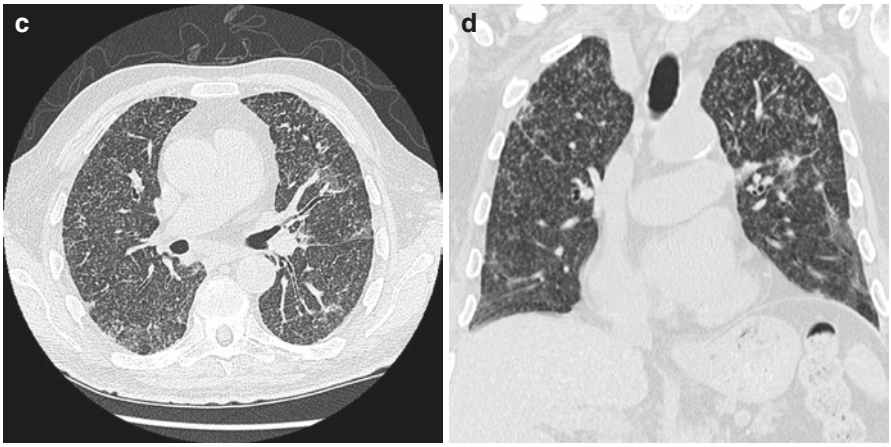

Fig. 8.13 (continued)

Bronchoscopy, Bronchoalveolar Lavage and TBB

- BAL: Microbiology: BAL fluid culture—negative aerobic growth. DNA testing: *Mycobacterium tuberculosis* complex—negative. Classic cultivation: Bactec MGIT cultivation negative.
- TBB: Multiple, in places confluent, epithelioid granulomas that are well bounded, of sarcoid appearance, rarely with small eosinophilic non-caseating necrosis. Some granulomas are located perivascularly, and also infiltrating and invading blood vessel walls, a finding corresponding to granulomatous vasculitis. In the special Ziehl-Neelsen staining, necrosis was found with numerous acid-fast rod-shaped bacilli.
- Conclusion: From a purely morphological point of view, according to the location and type of necrosis, and the presence of granulomas with insignificant sparse lymphocytic infiltrates in the vicinity, it would be appropriate to suggest that this is necrotising sarcoidosis. However, Ziehl-Neelsen staining revealed relatively numerous acid-fast rod-shaped microorganisms within the necrosis. This is probably an unusual manifestation of a mycobacterial infection, which is imitating sarcoidosis. The initial recommended therapy is treatment with antituberculous drugs. A biological examination using PCR was performed from the sample, indicating the presence of *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti* and BCG) was shown in the paraffin block.

8.3.1 Conclusion

The patient was admitted to be examined for pulmonary inflammation. Antibiotic treatment was without effect, thus bronchoscopy with BAL and TBB was completed. Histologically, a granulomatous disease with necrosis was detected, and

numerous acid-fast rod-shaped bacteria found using specific staining. PCR revealed *M. tuberculosis* complex positive. The findings are concluded as miliary tuberculosis. Combinations of four antituberculotics were administered, and the patient was transferred to the pulmonary clinic.

Note

- HRCT illustrated bilateral diffuse findings of multiple uniform, small, sharply bounded nodules. In this case, TB must be excluded initially. When considering the differential diagnosis, it is advisable to think of other processes with a diffuse image of nodules: metastases (usually larger in size), acute stage of HP (larger sized nodules, less sharply bounded, mosaic attenuation image, and air trapping are usually present), and finally the greatest imitator of diffuse lung pathologies, sarcoidosis (nodules mainly peribronchovascularly and on the pleura).
- Clinically, it is always necessary to think about the possibility of TB infection in elderly patients with a vague inflammatory process that is not reacting to ATB treatment.

8.3.2 Miliary Tuberculosis—What We Should Consider in Differential Diagnosis

1. Miliary dissemination of haematogenous metastases: The pathology is usually diffuse and also bilateral. Compared to nodules in miliary TB, metastases are usually of a larger size. The distribution is predominately basal. Clinically, a malignancy is usually already known (Fig. 8.14a, b).

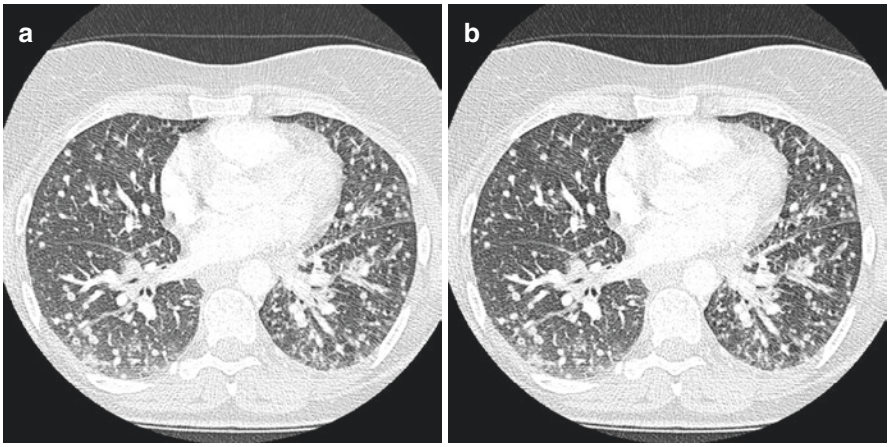

Fig. 8.14 (**a**) Miliary dissemination of haematogenous metastases: diffuse nodules. (**b**) Miliary dissemination of haematogenous metastases: diffuse nodules, predominately basally

2. HP (acute stage): Multiple fine opacities are equally distributed bilaterally, however in a centrilobular distribution. That means, they do not appear on the pleura (on interlobar fissures), in contrast to the random distribution in miliary TB. A mosaic image pattern is seen (Fig. 8.15a, b).
3. Sarcoidosis: In this case, it imitates random miliary distribution; however, the pathology is more uneven—some regions are affected more (dorsal) and some less (ventral). At the same time, nodules clearly prevail peribronchovascularly and on the interlobar fissures (beads on interlobar fissures) (Fig. 8.16a, b).

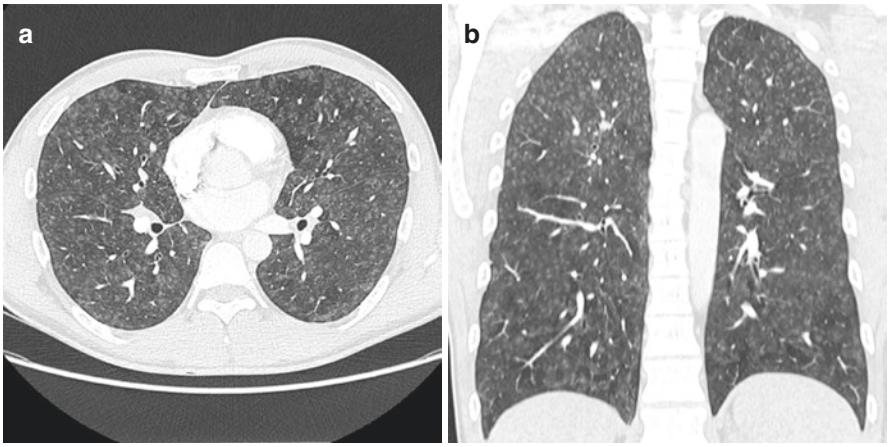

Fig. 8.15 (**a**) HP (acute stage): Multiple fine opacities are equally distributed bilaterally, however in a centrilobular distribution. (**b**) HP (acute stage), coronal reconstruction: Multiple fine opacities are equally distributed bilaterally, however in a centrilobular distribution

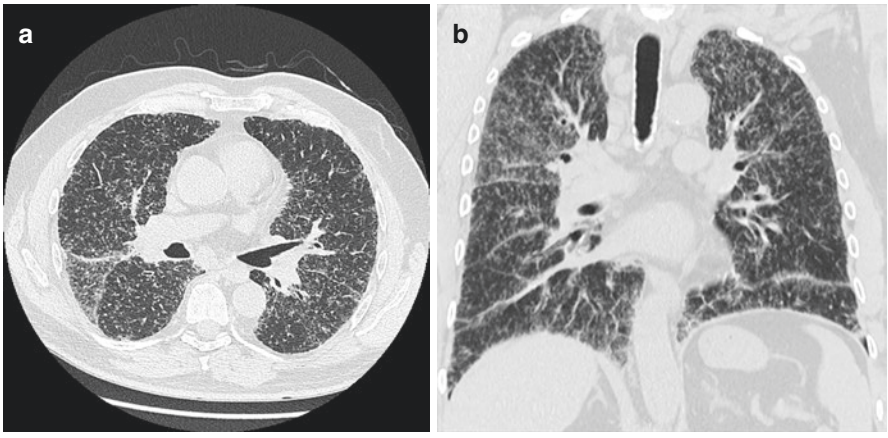

Fig. 8.16 (**a**) Sarcoidosis: nodules in perilymphatic distribution. (**b**) Sarcoidosis, coronal reconstruction: nodules in perilymphatic distribution

8.4 Hypersensitivity Pneumonitis (Acute Stage) I

Filip Ctvrtlik, Monika Zurkova, and Vladimira Lostakova

Male, 42 years old.

Patient presents after a 2-month history of exertional dyspnoea: cough and subfebrile.

Medical History

- A generalised pollen allergy, that affects the lungs, no treatment as yet

Occupational History and Exposure

- A mortgage broker, formerly worked as a fitness coach
- Lives in a flat. Used to have budgerigars in his childhood, and for 2 years keeps cockatiels.
- Smoking history: does not smoke cigarettes, smokes cigars occasionally

History of Present Complaint

- He complains of exertional dyspnoea that has been ongoing for 2 months, and a tickly cough, sometimes with coughing attacks and a feeling of chest pain. He has remained subfebrile (37–37.5 °C) during the whole time. He also claims weight loss of 15 kg in the past 3 months with a worsening appetite.

Objective Finding

- Vesicular breathing and basal crepitations.

Examination

Lung Functional Tests

- VC 4.27 L/76% (ref. v), FEV_1 3.61 L/82% (ref. v), FEV_1/VC 84% (ref. v), TLC 93%, DL_{CO} 36.4% (ref. v), K_{CO} 47.7% (ref. v.)
- A slight decrease in VC, with a normal value of FEV_1/VC and TLC index. A severe reduction of transfer factor and transfer coefficient

Radiology

- *Posteroanterior and lateral chest X-ray*: Diffuse fine nodules symmetrically distributed in both lobes.
- *HRCT of the lungs*: Multiple bilateral and evenly distributed fine nodules (opacities) centrilobularly. The posterior costophrenic angles are spared. The diagnosis would have been greatly supported by exhalation scans with the finding of air trapping (expiratory scans were not performed here because this was a CTA) (Fig. 8.17a–e).

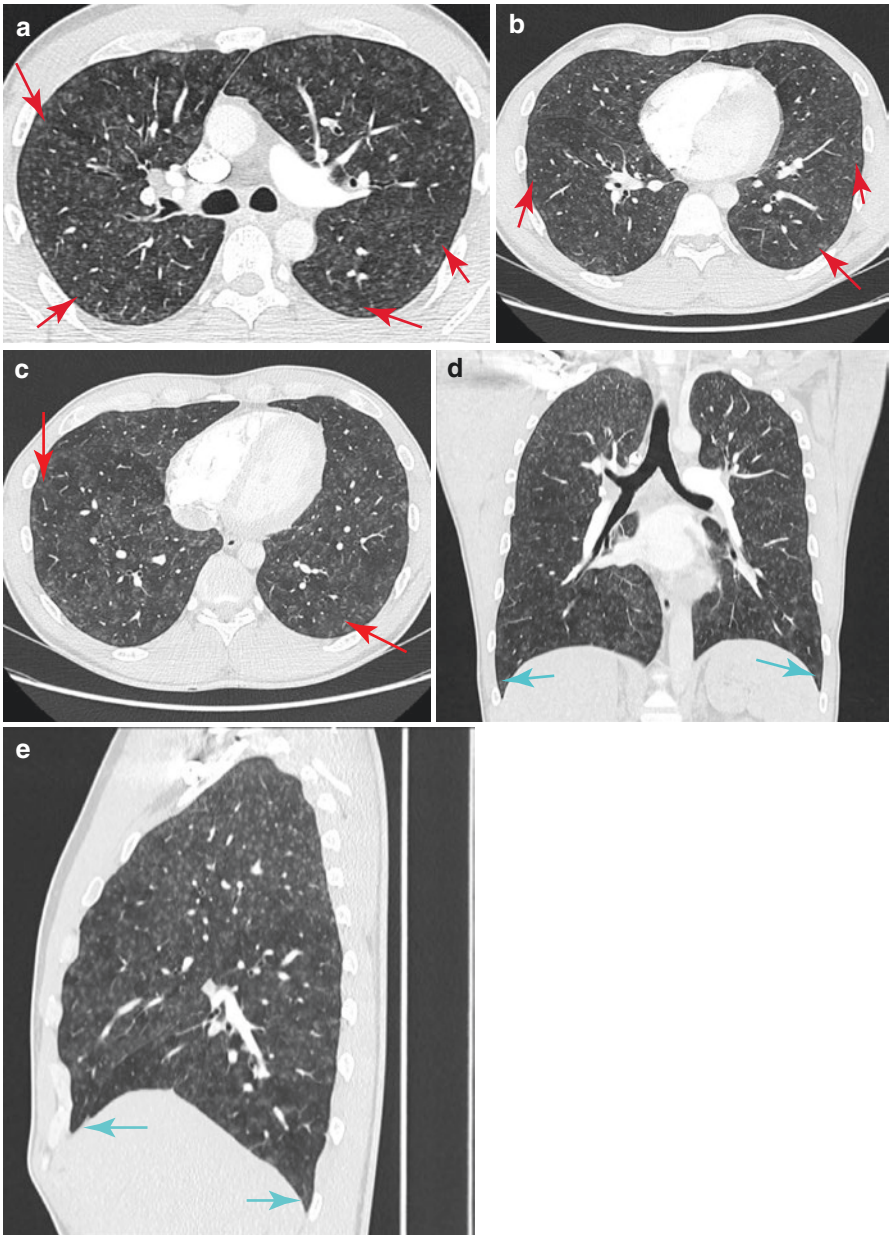

Fig. 8.17 (**a**) HRCT of the lungs: bilateral multiple fine nodules in centrilobular. (**b**) HRCT of the lungs: bilateral multiple nodules in centrilobular distribution. (**c**) HRCT of the lungs: bilateral multiple fine nodulations in centrilobular distribution. (**d**) HRCT of the lungs (coronal reconstruction): centrilobular nodules conserving costophrenic angles. (**e**) HRCT of the lungs (sagittal reconstruction): nodules conserving costophrenic angles

Auxiliary and Laboratory Examinations

- Biochemistry tests and blood count were in the normal ranges. An ECG and echocardiography were both normal.

8.4.1 Multidisciplinary Team and Differential Diagnosis

With the combination of clinical symptoms, subfebrile, coughing, a 2-month history of dyspnoea with an inducing antigen, and the HRCT findings of centrilobular fine diffuse symmetrical opacities, this indicates acute HP. Bronchoscopy with BAL and histological sampling are recommended.

Bronchoscopy, Bronchoalveolar Lavage, TBB

- *BAL*: Macrophages: 22%, lymphocytes: 59%, neutrophils: 15% eosinophils: 4%.
- *Diagnostic conclusion:* mixed alveolitis, and epithelioid cells.
- *TBB*: Lymphocytic infiltrates within the alveolar septa, with a finding of a small non-cohesive granuloma in one deposition. Fibrosis is not apparent. In other regions, there are multiple non-cohesive granulomas, lymphocytic pneumonitis, and chronic bronchitis. The image conforms to acute HP.
- *Microbiology* (*Mycoplasma* spp., *Chlamydia* sp., TB): negative.

8.4.2 Conclusion

The radiological findings, clinical presentation, and histopathological examinations are compatible with the diagnosis of acute HP. Corticosteroid therapy was administered with an initial dose of 40 mg prednisone, and to continue with a gradually reducing dose regime.

Note

In clinical practice, inflammatory infectious diseases are the most common cause of centrilobular GGO (nodules) in patients with acute symptoms. If symptoms are recurrent, or longer lasting (2 weeks to 6 months), it is first necessary to think of acute HP or the lepidic pattern of growth in carcinoma. The chronic stage of HP may imitate other fibrosing interstitial diseases on HRCT, e.g. UIP/IPF, connective tissue diseases, drug-induced disorder, asbestosis or sarcoidosis.

8.4.3 Hypersensitivity Pneumonitis (Acute)—What We Should Consider in Differential Diagnosis

1. Sarcoidosis: HRCT—Nodules in the perilymphatic distribution—present mainly on the pleura (beads on interlobar fissures), centrally and peribronchovascularly. Nodules are irregularly distributed, predominantly affecting the upper and middle lung fields (Fig. 8.18). Furthermore, enlarged nodes in the mediastinum are usually apparent.

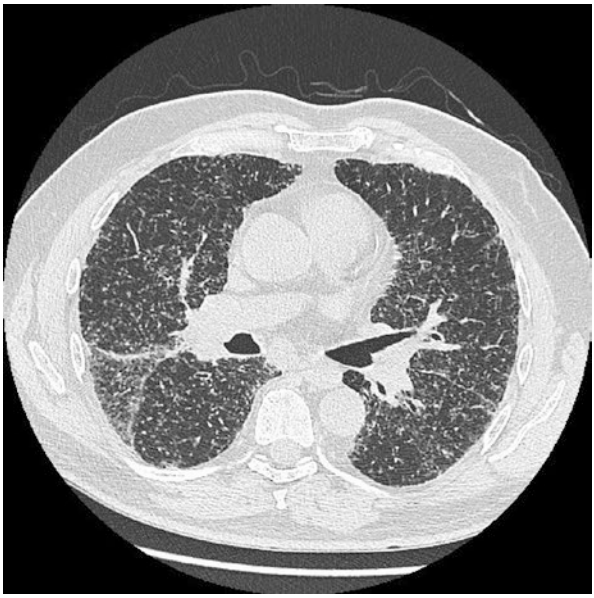

Fig. 8.18 Sarcoidosis: perilymphatic nodules

2. Silicosis: HRCT—Nodules in the perilymphatic distribution, symmetrically, mainly affecting the upper and middle lung fields. Furthermore, usually present are enlarged lymph nodes in the mediastinum with shell-like calcifications. Diagnosis is supported by past history of occupational exposure to silica dust (Fig. 8.19).
3. Miliary spread of TB: HRCT—Nodules in the random distribution, with diffuse symmetrical distribution in both lobes. Clinically, severe manifestations of inflammation are present, especially high fevers, profuse sweating, and cough, usually with blood (Fig. 8.20).
4. Infectious inflammatory disease with endobronchial dissemination—conditional to typical pathogens—(bronchopneumonia)—or mycobacterial infection (TB): HRCT—centrilobular nodules endobronchially, where the spread of infection usually creates tree-in-bud opacities. The finding is rather uneven and asymmetrical. In bacterial infections, consolidations predominate, which can merge to create larger areas. Post-primary TB distribution prevails cranially and cavitations may be present. Clinically, they are acute clinical manifestations that are accompanied by laboratory findings and variations in the blood count indicating inflammation (Fig. 8.21).
5. Infectious inflammatory disease dependant on atypical pathogens (*Mycoplasma* spp., *Chlamydia* sp., *Legionella* spp., *Pneumocystis jirovecii*, viruses): HRCT—bilateral symmetrical large regions of GGO predominate. *Pneumocystis* occurs particularly in immunocompromised individuals. Clinically, the diagnosis is supported by prominent overall symptoms and a positive microbiological finding (Fig. 8.22).
6. RB-ILD: HRCT—diffuse symmetrical bilateral non-significant opacities in the centrilobular distribution, predominating in the cranial parts of the lungs. It occurs in smokers (Fig. 8.23).

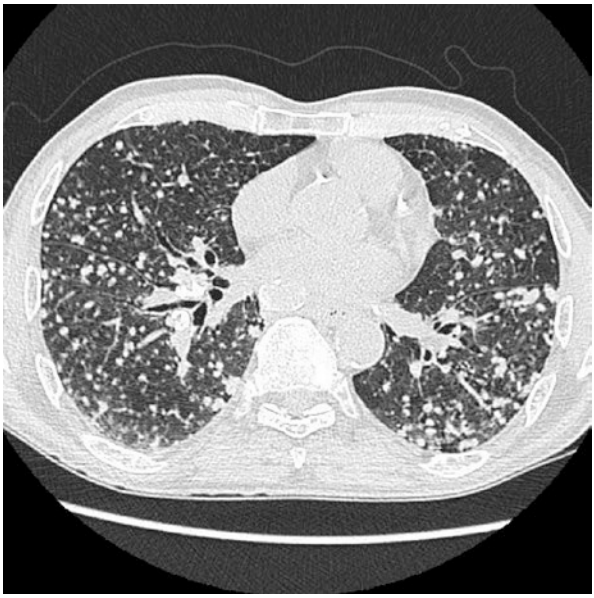

Fig. 8.19 Silicosis: perilymphatic nodules, enlarged lymph nodes with calcifications

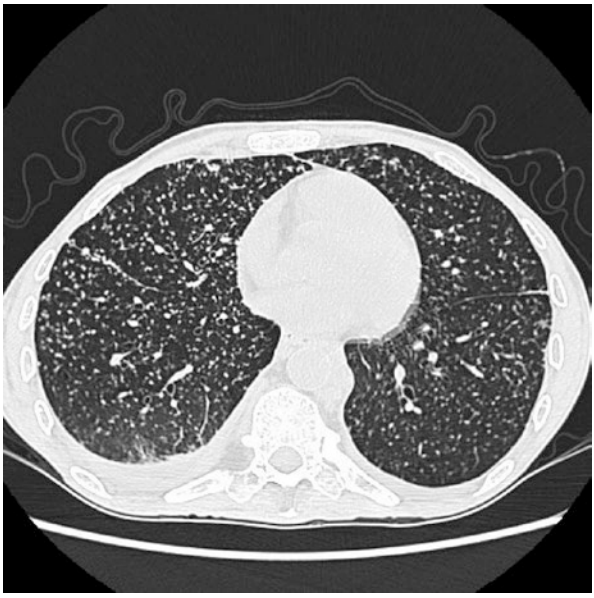

Fig. 8.20 Miliary spread of TB: Nodulations in the random distribution

7. Adenocarcinoma with lepidic growth: HRCT—the effect is uneven, often multifocal, and centrilobular opacities may merge into larger regions of GGO or consolidations. The possibility of adenocarcinoma would be indicated by the image of non-retreating "inflammatory infiltration" on an X-ray, which does not respond to antibiotics (Fig. 8.24).

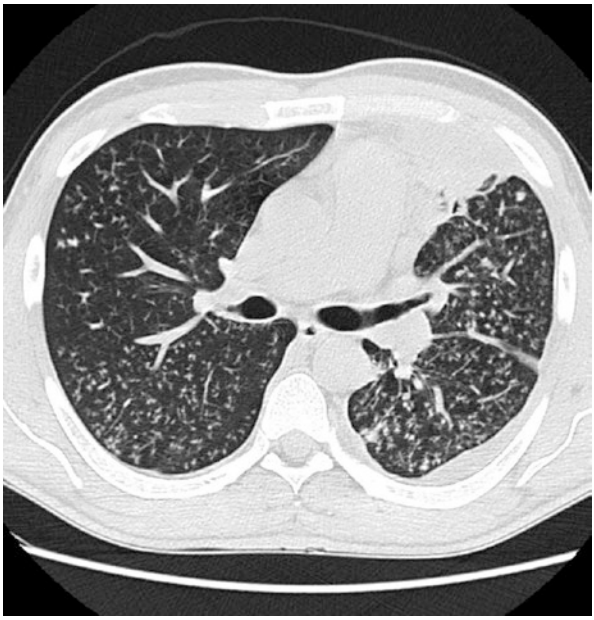

Fig. 8.21 Infection: centrilobular nodules create tree-in-bud opacities

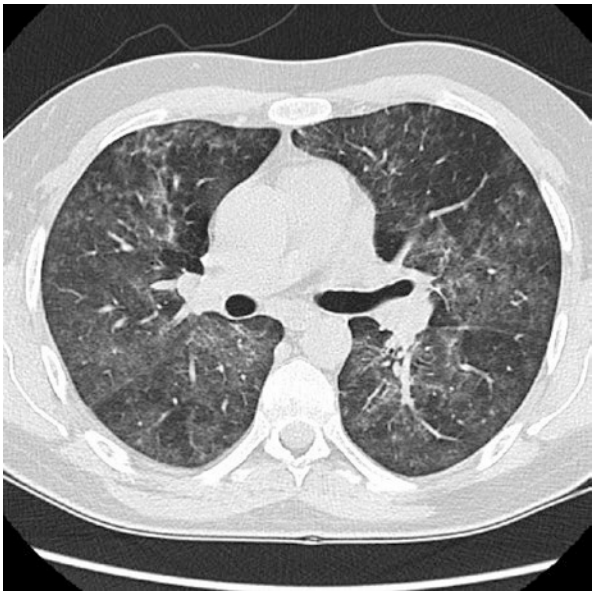

Fig. 8.22 Infection: patchy GGO

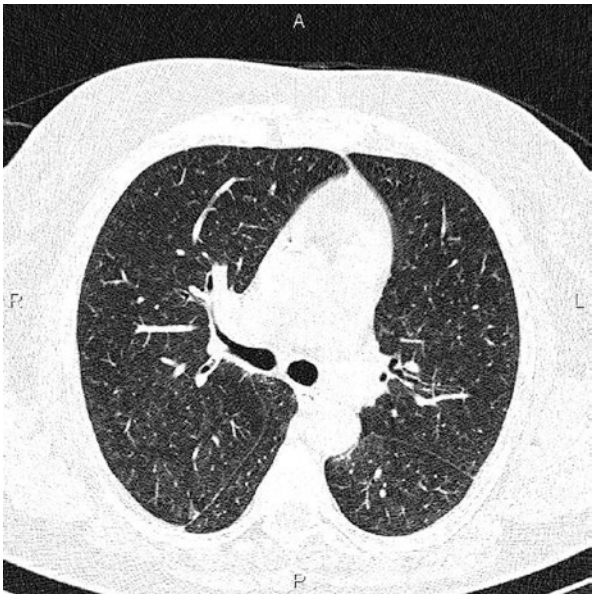

Fig. 8.23 RB-ILD: diffuse symmetrical bilateral centrilobular opacities

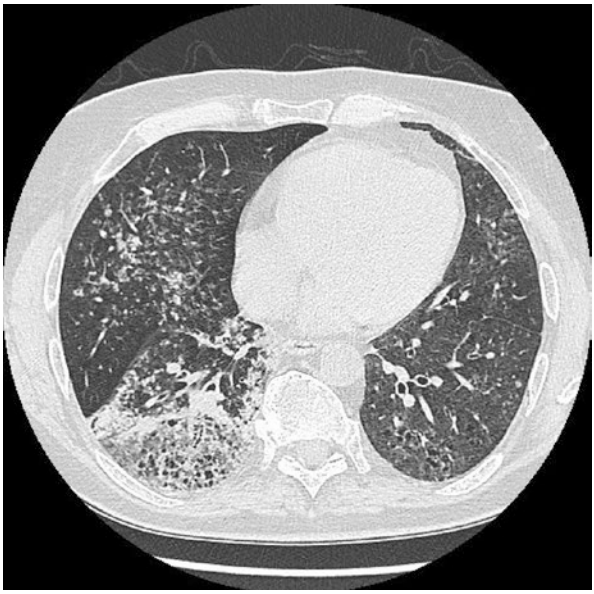

Fig. 8.24 Adenocarcinoma with lepidic growth: multifocal, and centrilobular opacities may merge into larger regions of GGO or consolidations, reticulations

8.5 Hypersensitivity Pneumonitis (Acute Stage) II

Filip Ctvrtlik, Monika Zurkova, and Vladimira Lostakova

Female, 33 years old.

Presenting with worsening breathing difficulties and fatigue.

Medical History

- Goitre
- Otherwise healthy until now

Occupational History and Exposure

- Physician

History of Present Complaint

- Three months ago, she came through the viral infection. Due to a persisting cough and being subfebrile, chlamydia was considered and therefore treated with antibiotics. The antibiotics did not help. She was examined at the department of respiratory medicine for persisting problems: cough with white sputum expectorate and body temperatures/subfebrile. Dominate symptoms were dyspnoea and fatigue. Her symptoms worsened during working hours while staying in an inspection room in the attic, where there is a ledge on which pigeons rest regularly, leaving a large quantity of their droppings.

Objective Finding

- Lung percussion resonant and vesicular breathing with no secondary phenomena (negative auscultation findings).

Examination

Lung Functional Tests

- Mild restrictive ventilatory disorder (FVC 2.80/73% (ref. v), TLC 3.96/72% (ref. v)), and a severe decrease in pulmonary diffusion capacity (DL_{CO} 38% ref. v).

Radiology

- *Posteroanterior and lateral chest X-ray*: Fine nodules diffusely in both lung lobes.
- *HRCT of the lungs*: Bilateral multiple fine nodules (opacities) in a centrilobular distribution (Fig. 8.25a–d).

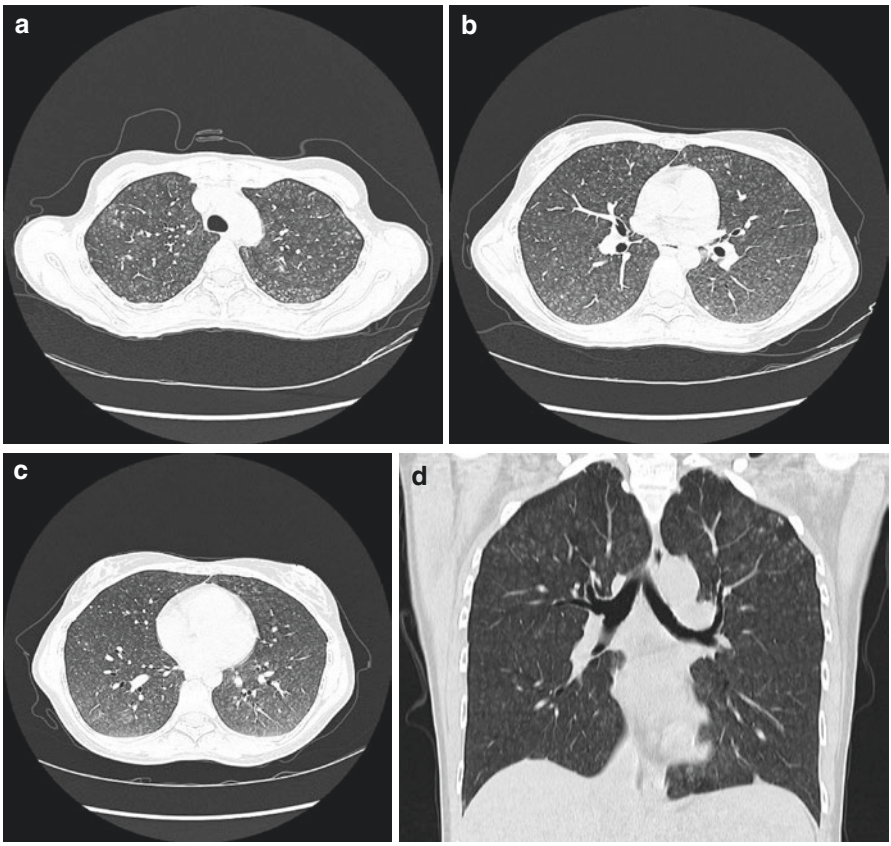

Fig. 8.25 (**a**) HRCT of the lungs: acute HP with multiple centrilobular nodules. (**b**) HRCT of the lungs: acute HP with centrilobular nodules, bare fissures. (**c**) HRCT of the lungs: acute HP with centrilobular nodules, small GGO areas. (**d**) HRCT of the lungs (coronal reconstruction): acute HP with centrilobular nodules in the whole lung

8.5.1 Multidisciplinary Team and Differential Diagnosis

Clinically and radiologically, this may be the acute stage of HP. A bronchoscopy with bronchoalveolar lavage and histological sampling is recommended.

Bronchoscopy, Bronchoalveolar Lavage and TBB

- The endobronchial finding was negative. A lingual BAL, TBLB from the right lower and middle lobes, and node biopsy were performed.
- BAL: Lymphocytes (47%), neutrophilic (7%) and eosinophilic alveolitis (3%), numerous epithelioid cells. Immunology: CD4/CD8 ratio = 0.97.
- Node biopsy: activated lymph nodes.

- TBB: granulomatous inflammation in the bronchial wall and peribronchial lung tissue, mostly with widespread granulomas or individual multi-nuclear cells. An infectious origin is not suspected. The initial consideration is HP.

8.5.2 Conclusion

A patient with an interstitial lung disease that was examined after a 3 month history of clinical symptoms. According to the examinations performed, HP was verified. The diagnosis was confirmed histologically from TBB. The disease was further evidenced by the clinical course and clinical history (worsening of the symptoms at work, and pigeons on the window ledge). This included high IgG values to feathers, faeces, and serum of the pigeons, radiological changes, and BAL fluid results including immunology, and the exclusion of other aetiology, e.g. infectious or systemic disease. Corticosteroid therapy with a gradual reducing dose was initiated. The patient's symptoms completely subsided, with the normalisation of functional parameters and a reduction of radiological patterns.

Note

- Antigen examination is a complementary test when determining the EAA diagnosis. Although these tests are less specific, they can greatly help to explain the inducing causes of the disease, as well as guide the treatment—the basic rule of which is the elimination of the inducing antigen.
- The chronic stage of the HP may imitate other fibrosing diseases of the interstitium on the HRCT, e.g. UIP/IPF, drug-induced disorder, connective tissue disease, asbestosis or sarcoidosis.

8.5.3 Hypersensitivity Pneumonitis (Acute)—What We Should Consider in Differential Diagnosis

1. Sarcoidosis: When considering the BAL fluid examination, both diseases illustrate lymphocytic alveolitis, but they differ in the predominance of the lymphocyte subpopulations. In sarcoidosis, CD4 lymphocytes predominate, and therefore the CD4/CD8 ratio in sarcoidosis is higher, at values above 3 for sarcoidosis to be precise (Fig. 8.26).
2. Silicosis: The diagnosis is supported by a history of occupational exposure to silica dust (Fig. 8.27).
3. Bronchiolitis: Most commonly infectious bronchiolitis—the clinical signs of inflammation and the tree-in-bud sign usually indicate this possibility (Fig. 8.28a, b).
4. Lymphoma: Clinically, B-symptoms may be present, and laboratory changes in the blood count with higher sedimentation levels and elevated LDH levels may occur. HRCT: most often multiple larger irregularly bounded nodules, masses or consolidations (Fig. 8.29).

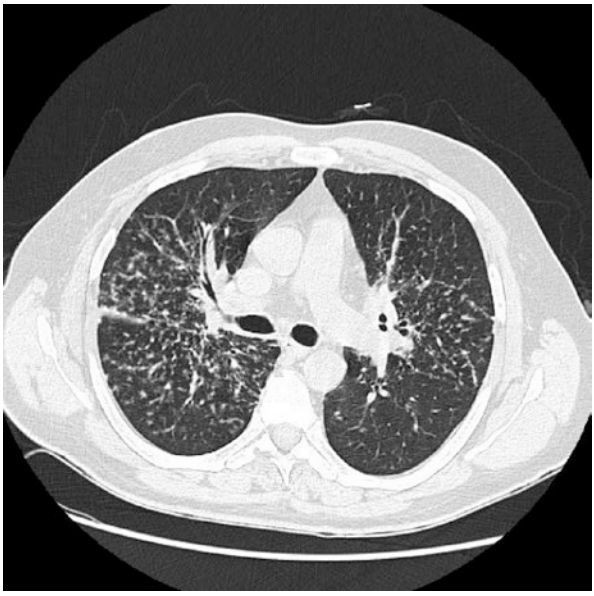

Fig. 8.26 Sarcoidosis: nodules in a perilymphatic distribution, mostly affecting the upper and middle lung fields

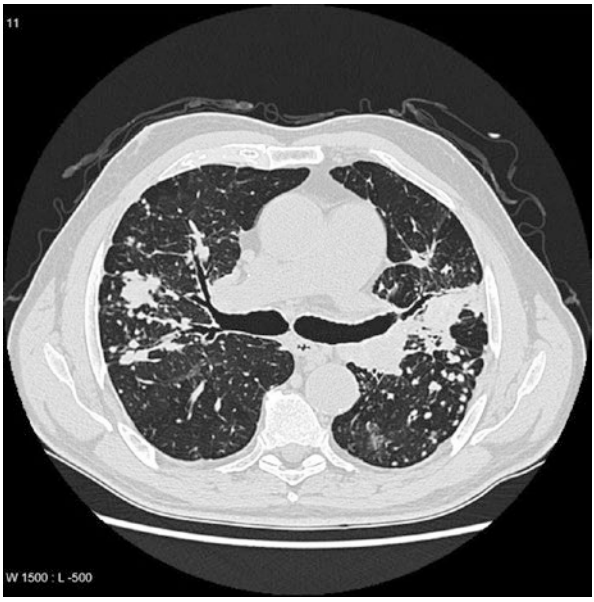

Fig. 8.27 Silicosis: nodules are in a perilymphatic distribution, symmetrically, affecting the upper and middle lung zones

5. Aspiration: Past medical history is important: Unconsciousness data (trauma, drowning), an oesophageal disorder in scleroderma, elderly status, dementia, alcoholism, etc. HRCT: centrilobular opacities, changes generally predominate in the dorsal and basal parts of the lungs (Fig. 8.30).

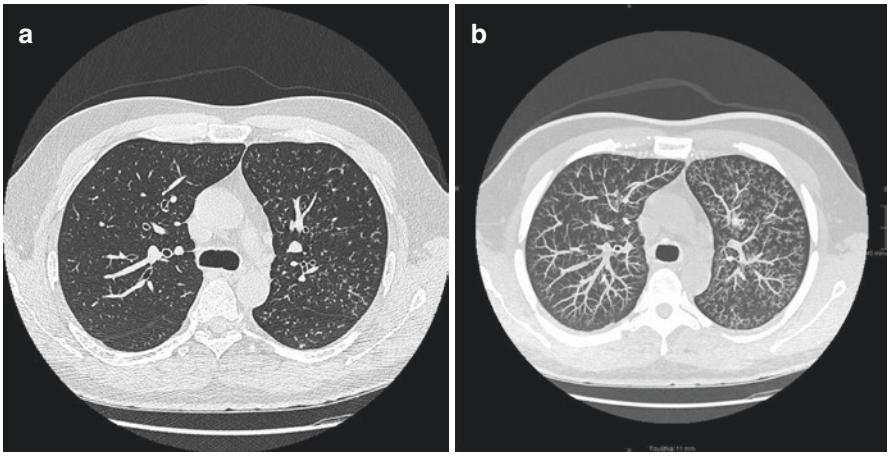

Fig. 8.28 (**a**) Bronchiolitis: nodules are in a centrilobular distribution where they create a "tree-in-bud" pattern. (**b**) Bronchiolitis (MIP reconstruction): nodules are in a centrilobular distribution where they create a "tree-in-bud" image

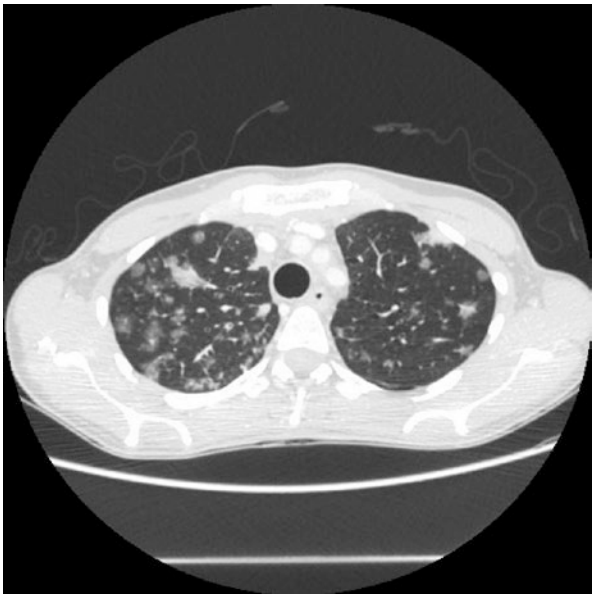

Fig. 8.29 Lymphoma: larger irregularly bounded nodules, masses or consolidations, some GGO

6. Cytomegalovirus infection: Occurs especially in immunocompromised individuals (after transplant, during immunosuppressive therapy, in AIDS, etc.). In patients after bone marrow transplant, it occurs early in the post-transplant period (30–100 days after). Here, the possibility of *Pneumocystis jirovecii* infection, which has a similar HRCT image, should be considered. HRCT: centrilobular nodules, bilateral symmetrical GGO conserving the lung peripheries (Fig. 8.31).

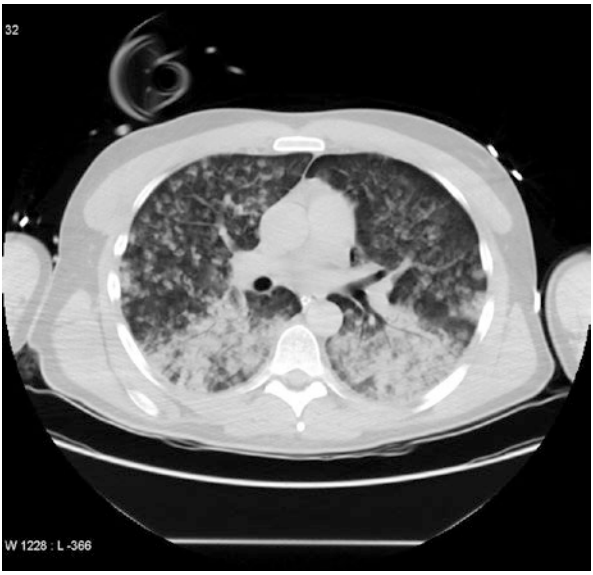

Fig. 8.30 Aspiration: centrilobular opacities, predominate in the dorsal parts of the lungs

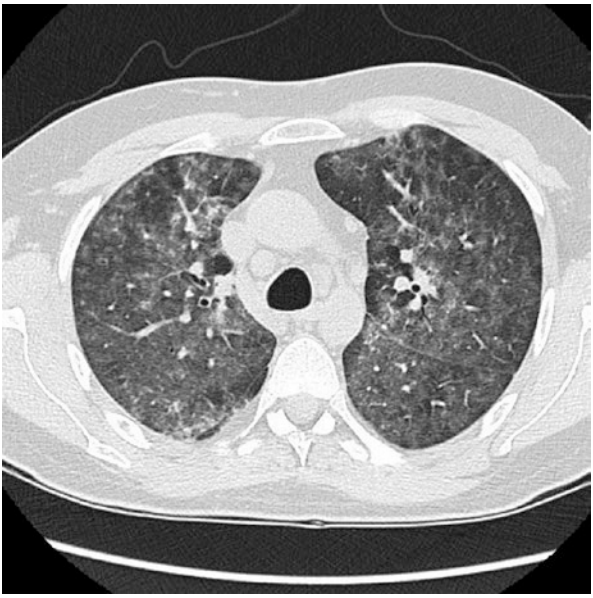

Fig. 8.31 Infection (cytomegalovirus): centrilobular nodules, bilateral symmetrical GGO conserving the lung peripheries

8.6 Berylliosis

Eva Kocova and Vladimir Bartos

Female, 52 years old.

Patient attending the Department of Respiratory Medicine, for her chest X-ray findings to be reviewed.

Medical History

- Insignificant, without long-term medications/therapy

Occupational History and Exposure

- Occupational exposure—For more than 20 years working in a very dusty environment—metal bending, glass polishing, and chemical management
- Smoking history: smokes 10 cigarettes a day since youth
- Traveling history—negative, she has never travelled outside Europe

History of Present Complaint

- She has been feeling mild exertional dyspnoea for several years, which is not worsening. She has a chronic dry cough and tends to get more tired after work. Previously, she was pyrexial, which is now resolved. She does not have joint problems, but has a chronic rash on her forearms and torso.

Objective Finding

- Vesicular breathing, without crepitations. On the skin of the forearms, underarms, torso, groin, thighs, and calves there is a light pink exanthema. In some places, there are red to purple-red exanthema with subcutaneous indolent nodules, subdermal, without fistula or defects.

Examination

Lung Functional Tests

- FVC 3.24 L/116% (ref. v), FEV_1 2.56 L/107% (ref. v), Tiff. 79%, TLC 5.69 L/121% (ref. v), RV 2.46 L/144% (ref. v), DL_{CO} 82% (ref. v), K_{CO} 1.37/82% (ref. v).
- Normal ventilation parameters, with no restrictive or obstructive ventilatory defect. Mild pulmonary hyperinflation. The transfer factor for CO is normal.

Radiology

- *Posteroanterior chest X-ray*: Multiple nodules in the upper and middle lung fields (Fig. 8.32).

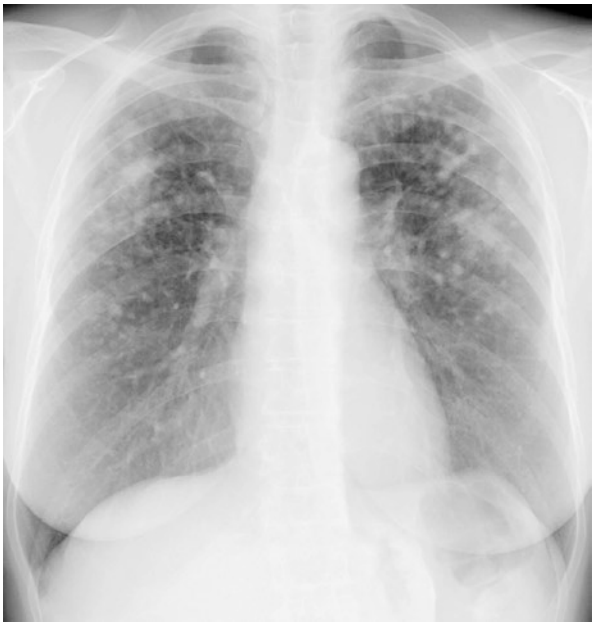

Fig. 8.32 Posteroanterior chest X-ray: multiple nodules in the upper and middle lung fields

- *HRCT of the lungs*: Multiple centrilobular and subpleural nodules, especially in the upper lobes and apical segments of the lower lobes. Some nodules are with bumpy calcifications, without necrosis. In the mediastinum, there are increased lymph nodes, some also with calcifications (Fig. 8.33a–d).

Bronchoscopy and Bronchoalveolar Lavage

- Normal endobronchial finding.
- BAL: 95% macrophages, 4% lymphocytes with CD8+ predominance, below 1% neutrophils and no malignant cells. There is no evidence of infection in the BALF, including no specific infection.

8.6.1 Multidisciplinary Team and Differential Diagnosis

There are nodular lesions affecting the pulmonary parenchyma, with an increased number of mediastinal nodules. According to HRCT, this initially appears as pneumoconiosis. Also noted is a history of a hazardous occupational exposure. In the differential diagnosis, it is important to also consider atypical sarcoidosis, although the findings in the BAL are not typical for this.

The conclusion of the MDT: Clinically and radiologically, this is probably pneumoconiosis. It is recommended to perform surgical verification of the lung pathology.

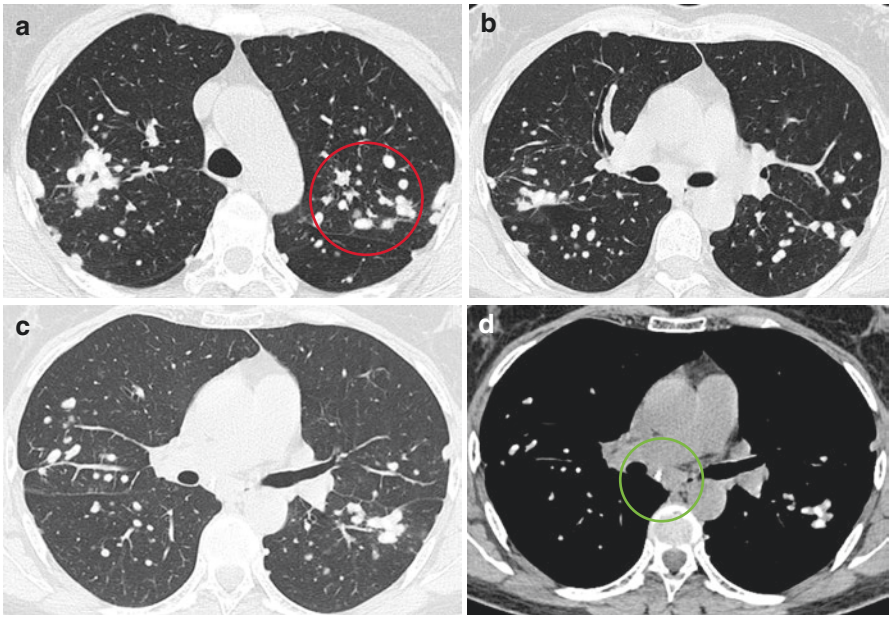

Fig. 8.33 (**a**) HRCT of the lungs: multiple nodules in the perilymphatic distribution. (**b**) HRCT of the lungs: multiple nodules in the perilymphatic distribution, mainly on fissures. (**c**) HRCT of the lungs: multiple nodules in perilymphatic distribution, and calcified mediastinal nodes. (**d**) HRCT of the lungs (mediastinal window): multiple nodules with calcifications, and calcified mediastinal nodes

VATS—Histological Verification of the Lung Disease

- The nature of the pulmonary lesions is typical for pneumoconiosis, probably with silicosis. An unusual finding is the presence of non-caseating necrosis. Staining for infectious agents is negative.

Auxiliary and Laboratory Examinations

- QuantiFERON-TB Gold test—negative, Mx II—negative, SACE and soluble IL-2 receptor are not pathologically increased. The blood count and biochemical examinations of the serum are normal, with no signs of inflammation. Serology for granulomatous infections are negative (brucellosis, tularaemia, toxocarosis, toxoplasmosis, lues, etc.), and also negative for HIV. Repeatedly, SCTD or an immunodeficiency has not been identified. An ultrasound, CT, and MRI of the abdomen were all normal, apart from a 6 cm haemangioma identified in the liver. The oncological screening was negative, with negative tumour markers. The microbiological culture of biological materials and biopsy were negative.
- Skin Examination: Further skin biopsies have been performed due to the resistance to regular treatment, and granulomatous inflammation was repeatedly found.

8.6.2 Conclusion

Due to the rare findings, the histological samples of the lung and skin, and the HRCT of the lungs (where the size and number of nodules progressed over 3 years) were consulted this case at the Mayo Clinic, where the findings were concluded as berylliosis. In a retrospective analysis, it was confirmed at the department that there was evidence of beryllium, at low concentrations, in compounds used in the past during glass melting. The lymphoblastic transformation test after beryllium exposure has not been performed (not available in Czech Republic). It was recommended to the patient to remove herself from the risk, i.e. change of occupation. Thus, the occupational disease was recognised. Now, the patient is without any functional progression, and there is no further advancement of the findings on imaging methods.

Note
Berylliosis is a rare pulmonary disease, usually with a chronic course, caused by chronic beryllium exposure. The HRCT image corresponds with pneumoconiosis—nodules in the centrilobular and perilymphatic distribution, especially in the upper lobes, often with calcifications, and mediastinal lymphadenopathy with calcifications. In the later stages, there may be possible reticulations, traction, and larger conglomerates with fibrosis.

8.6.3 Berylliosis—What We Should Consider in Differential Diagnosis

1. Pulmonary sarcoidosis: Nodularities in the perilymphatic distribution, especially in the central part of the lungs, lymphadenopathy in the mediastinum and pulmonary hila with calcifications—differential diagnosis is not possible based on the HRCT image alone (Fig. 8.34).

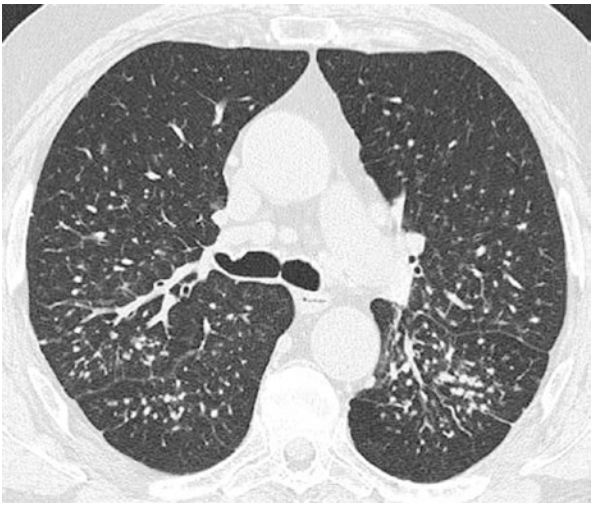

Fig. 8.34 Sarcoidosis: Nodules in the perilymphatic distribution

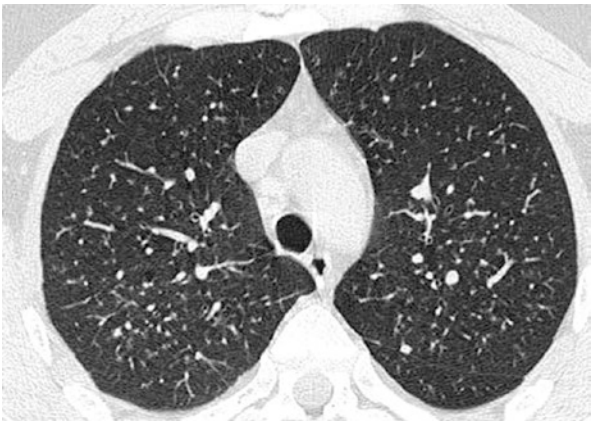

Fig. 8.35 Pneumoconiosis: perilymphatic nodules

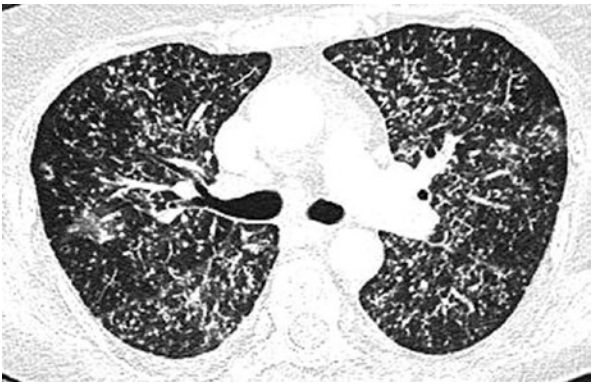

Fig. 8.36 Miliary TB: nodules in random distribution

2. Other pneumoconiosis: The HRCT finding is similar, and with the image alone it is not possible to make a differential diagnosis (Fig. 8.35).
3. Miliary pulmonary tuberculosis: Multiple nodules of uniform size and distribution (Fig. 8.36).

8.7 Diffuse Pulmonary Ossification

Martina Sterclova, Jana Votrubova, and Eva Kocova

Male, 61 years old.

The patient was sent from an outpatient clinic to be examined for suspected miliary tuberculosis. He was examined for half a year for lasting cough and exertional dyspnoea.

Medical History

- Depression

Occupational History and Exposure

- Optometrist—grinding glass lenses
- Worked in subway excavation, lives with family, no pets, and his flat has a dry environment
- Smoking history: has not smoked for 6 years, before that smoked 20 cigarettes a day for 20 years
- Medication history: bupropion, clonazepam, mirtazapine

History of Present Complaint

- He has observed about half of the year, for a cough with a white expectorate, and exertional dyspnoea. He denies fever and sweating, weight loss is not observed, he has no joint difficulties, and denies digestive symptoms.

Objective Finding

- Bilateral vesicular breathing, with slight crepitations on the right above the base

Examination

Lung Functional Tests

- FVC 3.19 L/72% (ref. v), VC_{max} 3.26 L/71% (ref. v), FEV_1 2.32 L/67% (ref. v), FEV_1/FVC 73%, TLC 4.61 L/59% (ref. v), DL_{CO} 4.84/49% (ref. v)
- Mild reduction in forced vital capacity, a moderate restrictive ventilatory disorder, and a moderately reduced transfer factor for CO

Radiology

- *HRCT of the lungs*: Fine diffuse random calcifications with predominance basally. This pattern is often seen on a CT in patients after infections or in pulmonary hypertension (Fig. 8.37a–c).
- The patient's history is reviewed. There are unilateral TB calcifications. Calcifications in malignancies are coarser.

Bronchoalveolar Lavage

- *Mycobacterium tuberculosis*—microscopy and culture tests are negative, and PCR is also negative. The BAL contains a mixture of phlegm, cilia, foamy macrophages and erythrocytes. Alveolar macrophages 88%, neutrophils 5%, lymphocytes 6% and eosinophils 1%.

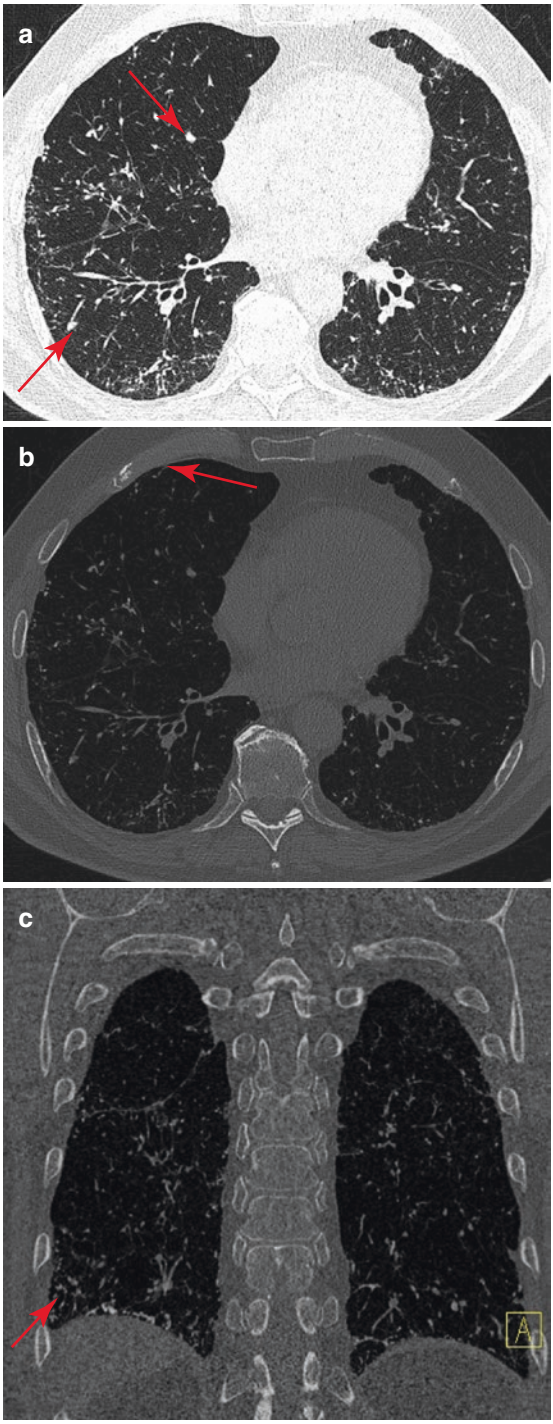

Fig. 8.37 (**a**) HRCT of the lungs: fine diffuse random ossifications in pulmonary parenchyma. (**b**) HRCT of the lungs (bone window): fine diffuse random ossifications in lung parenchyma. (**c**) HRCT of the lungs (bone window, coronal reconstruction): fine diffuse random ossifications with predominance basally

Autoantibody Screen, and Exposure—Specific IgG, Calcium Metabolism

- ANA neg, ENA neg, RF neg, ANCA neg; specific IgG in serum—the values are generally low and do not indicate a significant source of exposure. Serum calcium is normal, and the standard excretion of Ca/24 h in urine is within the standard range.

8.7.1 Multidisciplinary Team and Differential Diagnosis

The patient has a small lung nodules, which apparently is not sarcoidosis. According to CT, even reticulations are in the lower lobes; however, the lymph nodes are not enlarged. The finding is unclear and requires a VATS biopsy.

VATS and Histology

- There are numerous ossifications and calcification deposits, including within the fatty bone marrow. Unambiguous siliceous crystals in the given material, that are not found in polarised light. The distribution of changes topographically in the collected and examined sample does not clearly correspond to silicosis.

Endocrinological Examination

- Secondary hyperparathyroidism with significant vitamin D deficiency, however, there are calcification of the pulmonary interstitium. Renal failure is not described.

MRI of the Brain

- Supratentorially in the white matter, there are small regions of nonspecific gliosis paraventricularly, and moderate cortical atrophy. The finding is not typical for cerebral sarcoidosis.

8.7.2 Conclusion

- Diffuse pulmonary ossification. Sarcoidosis, silicosis or an endocrine aetiology is not identified.
- Treatment—only observation.

8.7.3 Pulmonary Ossification and Calcification

In pulmonary ossification, the formation of bony tissue with or without bone marrow occurs in the pulmonary parenchyma. Etiologically, pulmonary ossification can be divided into idiopathic or ossifications complicating a pre-existing disease.

Idiopathic pulmonary ossification is a rare disease characterised by exertional dyspnoea and cough.

On the chest X-ray of these patients, reticulonodulations in the lower lung fields are described.

Ectopic calcification in the lung can be subdivided into metastatic, dystrophic and idiopathic. Metastatic calcification affects undamaged pulmonary tissue (diffuse affection is referred to as a pumice lung), and dystrophic calcifications involve tissue affected by a pathological process. Idiopathic calcifications accompany pulmonary alveolar microlithiasis (Table 8.1).

Table 8.1 Pulmonary ossification

Idiopathic pulmonary ossification	
Pre-existing lung disease	Idiopathic pulmonary fibrosis Acute respiratory distress syndrome Chronic obstructive pulmonary disease Sarcoidosis Histoplasmosis Tuberculosis Metastases of melanoma Metastases of osteogenous sarcoma
Pre-existing cardiac disease	Mitral stenosis Chronic left-sided heart failure Idiopathic hypertrophic subaortic stenosis
Other diseases	Primary and secondary hyperparathyroidism Hypervitaminosis D Pyloric stenosis with alkalosis
Metastatic pulmonary calcifications	
Benign	Chronic renal insufficiency, dialysis Orthotopic liver transplant Primary hyperparathyroidism Hypervitaminosis D Excessive intake of calcium and vitamin D Osteopetrosis Paget's disease
Malignant	Parathyroid carcinoma Multiple myeloma Lymphoma, leukaemia Squamous cell carcinoma of the hypopharynx Synovial sarcoma Breast cancer Choriocarcinoma
Dystrophic pulmonary calcifications	
Granulomatous lung diseases	Infections: histoplasmosis, coccidioidomycosis, tuberculosis Sarcoidosis
Viral infections	Varicella
Parasitic infections	Paragonimiasis Pneumocystosis
Amyloidosis	
Lung vascular calcifications	Vascular grafts Pulmonary hypertension Increased flow through the pulmonary vascular system hemosiderosis
Pneumoconioses, silicosis	

Note

- Nodular ossifications are usually demonstrated in patients with cardiac disease.
- Dendriform ossification is more often described in patients with a pre-existing lung disease and accompanies also idiopathic pulmonary ossification.
- Idiopathic pulmonary ossification should be considered in the differential diagnosis in patients with minimal difficulties, subpleural reticulonodulations on the chest HRCT, and an indolent course over time.

8.7.4 Diffuse Pulmonary Ossification—What We Should Consider in Differential Diagnosis

1. Miliary tuberculosis: Calcifications can be in randomly distributed nodules (Fig. 8.38).
2. Pneumoconiosis: The nodules are especially in the upper pulmonary fields, and may contain calcifications which are also in the mediastinal and hilar nodules (Fig. 8.39).

These would also come into consideration: calcified lung metastases.

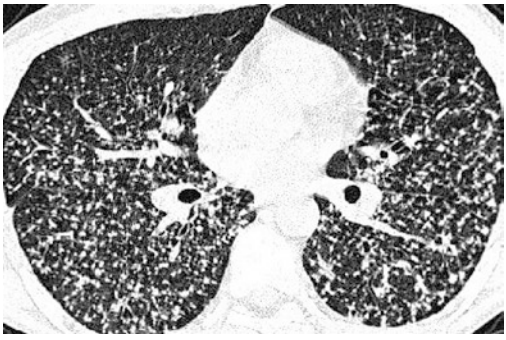

Fig. 8.38 Miliary TB: Calcifications in randomly distributed nodules

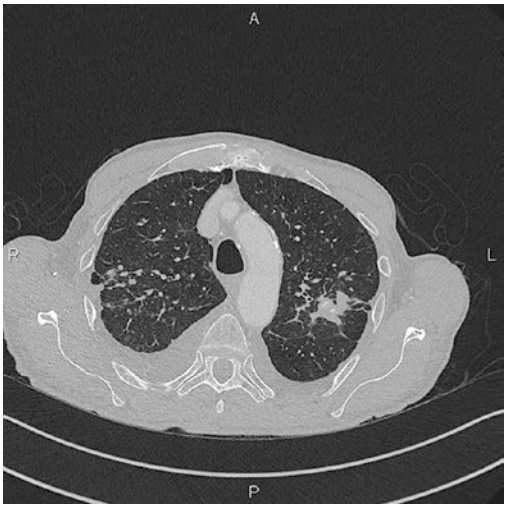

Fig. 8.39 Pneumoconiosis: Perilymphatic nodules in the upper pulmonary fields, with calcifications

8.8 Alveolar (Pseudoalveolar) Sarcoidosis

Eva Kocova and Vladimir Bartos

Female, 30 years old.

The patient referred by the GP to be examined at a pulmonary outpatient department for suspected metastatic neoplasia.

Medical History

- Epilepsy since the age of 11

Occupational History and Exposure

- Waitress, in a smokey environment
- Smoking history: Used to smoke 30 cigarettes daily from the age of 15, but has now not smoked for 2 months. Alcohol and drug history: alcohol and marijuana occasionally

History of Present Complaint

- About a month ago, she felt a lump above her clavicle. According to an ultrasound examination, the suspicion of a neoplastically altered node has been expressed. Subjectively, the last months she has been feeling as if there is a weight on her chest. Sometimes she coughs and expectorates yellow phlegm. There are no issues on exertion, except she feels very tired. She denies sweating, and she does not have any significant dyspnoea.

Objective Finding

- A palpable, indolent, firm, supraclavicular node. Vesicular breathing, no crepitations, patent airways, and no other pathology.

Examination

Lung Functional Tests

- Normal ventilation, without an obstructive or restrictive ventilatory disorder
- FVC 3.90 L/97% (ref. v), FEV_1 3.25 L/93% (ref. v), Tiff. 83%, MEF50 93% (ref. v), TLC 5.93 L/105% (ref. v), RV 1.28 L/80% (ref. v)
- A slight decrease in diffusing capacity for CO has been indicated (DL_{CO} 9.32/71% (ref. v) and K_{CO} 1.41/78% (ref. v))

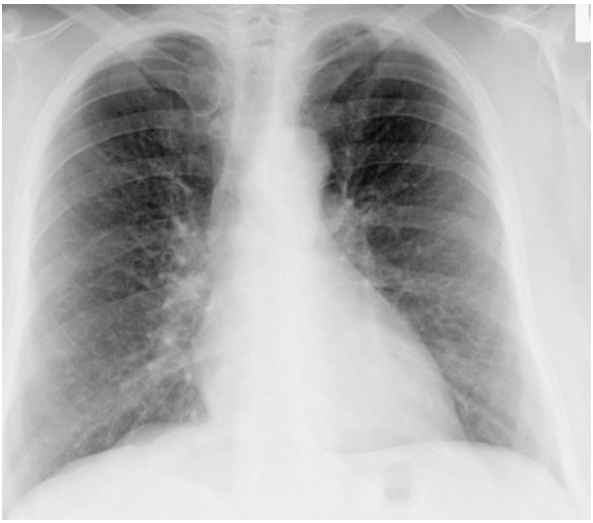

Fig. 8.40 Posteroanterior chest X-ray: multiple patchy shadows in both upper and middle lung fields

Radiology

- *Posteroanterior chest X-ray*: Bilateral multiple patchy shadows, more to the right. Bilateral hilar enlargement. The transverse diameter of the heart is not expanded, and there is no pulmonary congestion (Fig. 8.40).
- *HRCT of the lungs*: Bilateral and peribronchial multiple regions of GGO to consolidations, with air bronchogram, more on the right. No decay or no calcifications. The posterior costophrenic angles are without pathology. In the mediastinum and pulmonary hila, there are enlarged lymph nodes (Fig. 8.41a–f).

8.8.1 Multidisciplinary Team and Differential Diagnosis

Findings of multiple consolidations located peribronchially, without nodularities. In places, the "Atoll sign" (reversed halo sign) is seen. According to HRCT and the patient's history, there is a suspicion of haemato-oncological disease. In the differential diagnosis, sarcoidosis or an infectious aetiology of the symptoms is considered.

The conclusion of the MDT: Clinically and radiologically, it is recommended to perform an ultrasound of the abdomen, bronchoscopy with BAL and TBB from the right upper lobe, including an examination of urine and blood. Also indicated is identifying calcaemia, excluding tuberculosis, extirpation of the supraclavicular node, and a mammographic examination.

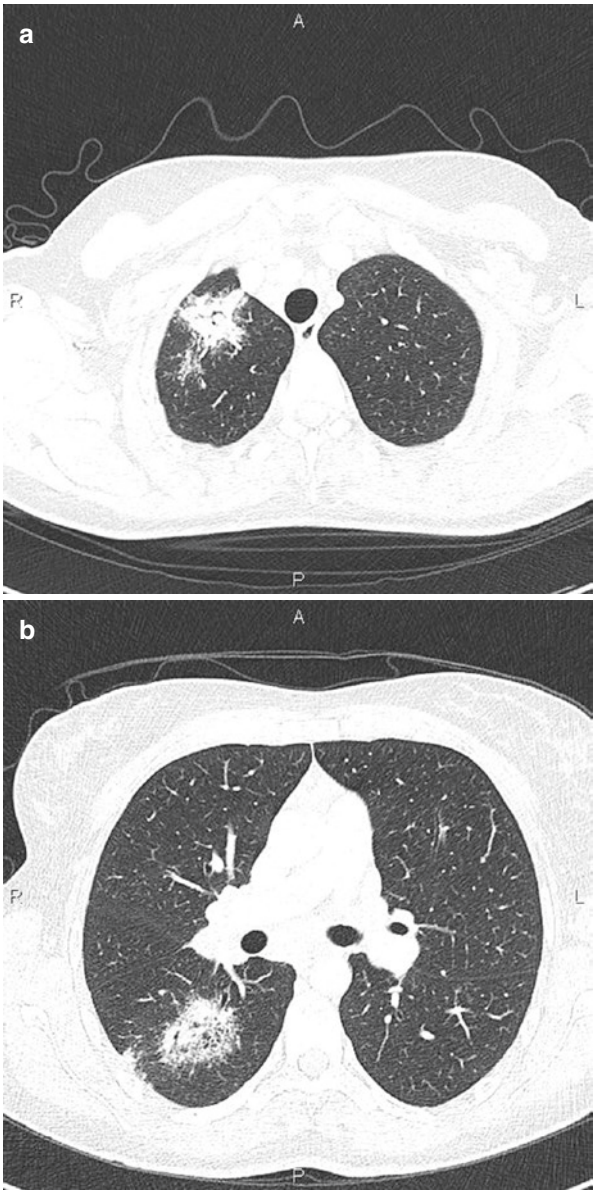

Fig. 8.41 (**a**) HRCT of the lungs: consolidation with air bronchogram in the right upper lobe. (**b**) HRCT of the lungs: consolidation with air bronchogram in the right lower lobe. (**c**) HRCT of the lungs: bilateral GGO and consolidation. (**d**) HRCT of the lungs: normal finding in the posterior costophrenic angles. (**e**) HRCT of the lungs (coronal reconstruction): a clearly expressed Atoll sign—GGO surrounded by consolidation. (**f**) HRCT of the lungs (coronal reconstruction): consolidations and GGO in both lungs

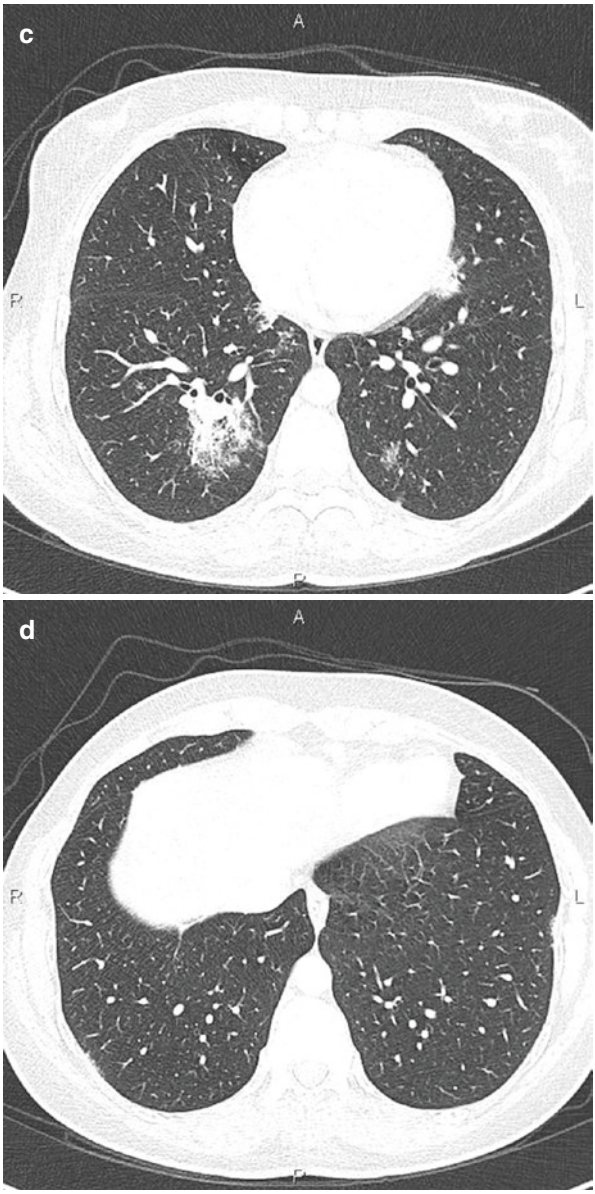

Fig. 8.41 (continued)

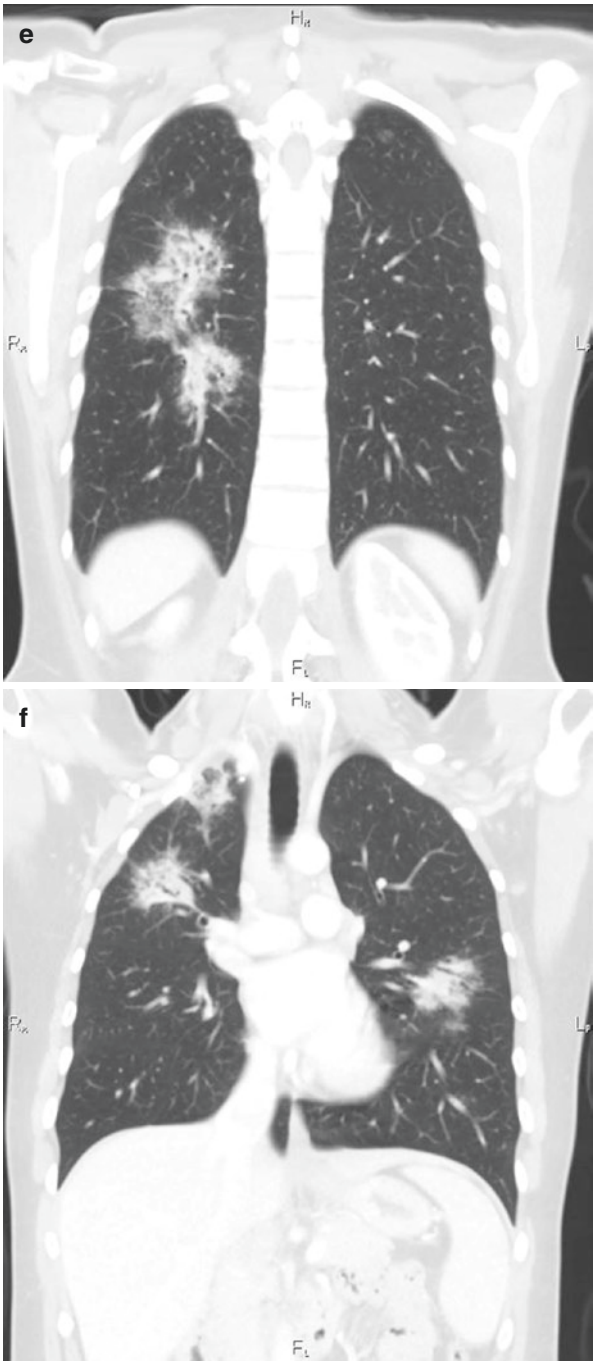

Fig. 8.41 (continued)

Auxiliary and Laboratory Examinations

- *Abdominal ultrasound*: multiple mesenteric lymphadenopathies without any other pathology
- *Mammographic examination*: negative
- Tuberculosis is excluded (Mx II—negative, IGRA tests—negative, and PCR and cultivation from BAL fluid—negative)
- *ENT examination*: normal findings, *supraclavicular node sampled*—histologically granulomatous inflammation without necrosis, and morphologically of the character of sarcoidosis
- *Echocardiography*: normal
- *Laboratory*: normal values of blood count and biochemical parameters, a low indication of inflammation, and normal SACE values. Hypercalciuria with normocalcaemia was detected

Bronchoscopy, Bronchoalveolar Lavage and TBB

- Normal finding in bronchoscopy.
- BAL: a multicellular sample with mostly lymphoid cells (31%—mainly T lymphocytes with a clear predominance of CD4+ T helper lymphocytes (83%), and the CD4+/CD8+ immunoregulation index was 5.9%. Neutrophils 1% and macrophages 66%.
- TBB revealed granulomatous inflammation without necrosis, morphologically with the nature of sarcoidosis. Culture and PCR for bacteria (including for TB) from the BAL fluid was negative.

8.8.2 Conclusion

According to the results of the BAL, TBB, histology and multiple GGO, the findings correspond to sarcoidosis, and a malignancy was not confirmed. The pulmonary findings on the HRCT indicate a type of alveolar (pseudoalveolar) sarcoidosis. A chest X-ray supported that the disease has slightly progressed, and therefore corticosteroid therapy was initiated with a beneficial effect (with regression of X-ray findings).

Note

- Pulmonary sarcoidosis is most often manifested by nodules in the perilymphatic distribution.
- The rare form is so-called alveolar (pseudoalveolar) sarcoidosis, which is characterised by the presence of GGO on the HRCT, known as the reversed halo sign (Atoll sign), with the arrangement of a central focal region of GGO surrounded by consolidations peribronchially. Also, it is not rare, even in this form, to find a galaxy sign, which is typical for sarcoidosis.

8.8.3 Alveolar (Pseudoalveolar) Sarcoidosis—What We Should Consider in Differential Diagnosis

1. Atypical infections: based only on a radiological image, it cannot be reliably distinguished (Fig. 8.42).
2. Organising pneumonia: typically, wispy peribronchial consolidations (Fig. 8.43).
3. Haematooncological disease: i.e. leukaemia—it is most often presented as consolidations of the pulmonary parenchyma, ground glass opacities, with no perilymphatic nodules. Past medical history is important however, it cannot be distinguished based only on the radiological signs (Fig. 8.44).

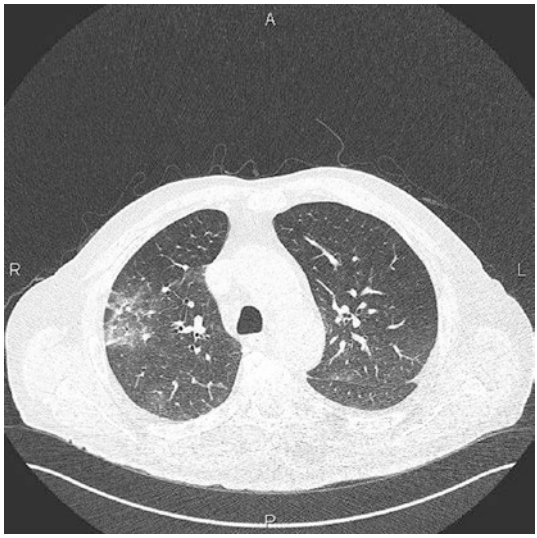

Fig. 8.42 Infection: GGO in the right upper lobe

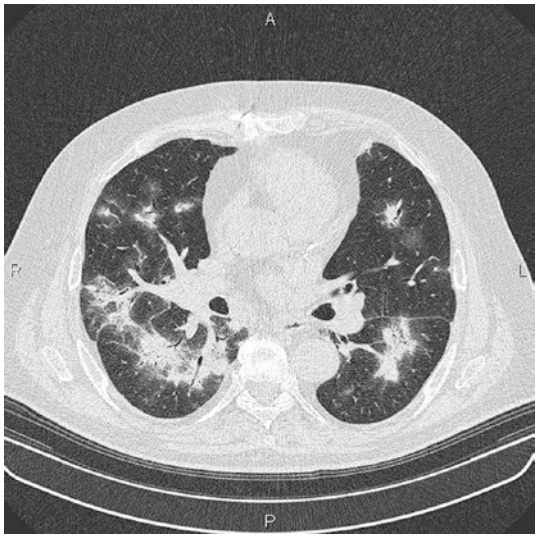

Fig. 8.43 Organising pneumonia: band-like consolidations

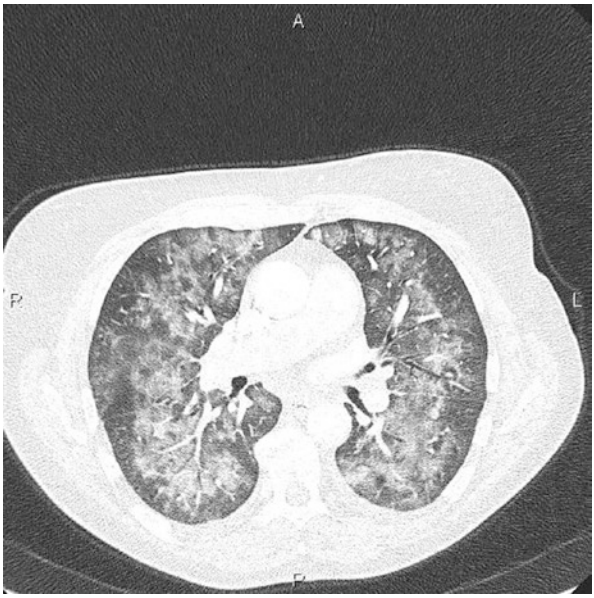

Fig. 8.44 Leukaemia: patchy areas of GGO in both lungs

8.9 Carcinomatous Lymphangiopathy II

Filip Ctvrtlik, Vladimira Lostakova, and Monika Zurkova

Male, 73 years old.

The patient presents with dyspnoea and a cough, a pressure in the chest, and weight loss.

Medical History

- Drug and alcohol withdrawal treatment in 2007
- Former smoker now stopped, he used to smoke up to 20 cigarettes a day for 55 years till 12/2017

Occupational and Social History

- In the past, he worked as an architect. He lost his job due to his drug and alcohol dependence.
- He is now an artist (a painter) and lives alone in a dormitory.

History of Present Complaint

- The patient was referred for examination by his GP, where he was first investigated on 01/2018, for increasing breathing difficulties (now even at minimal

exertion), a dry cough and a history of weight loss of 10 kg in 2 months. He reported chest pain combined with a feeling of pressure in the chest, severe pain in the back and pain in all the large joints. He reported no haemoptysis. He was treated with antibiotics, which were without any beneficial effect. For these reasons, his GP sent him for further investigations at the pulmonary department. A chest X-ray was performed, and was found to have pathological findings, leading a radiologist to suspect tuberculosis. The patient was admitted for examinations and therapy. Based on his past medical history, it was found that in 08/2016, he had observed swelling of the left breast, which he believed was a lipoma, and did not go for examination.

Objective Finding

- Regular cardiac rhythm and heart sounds. Lung percussion is resonant, with vesicular breathing without secondary phenomena.
- A palpable firm resistance in the left breast, and nipple destruction. The lower extremities are without oedema.

Examination

Lung Functional Tests
- This examination was not performed due to a specific suspected disease.

Auxiliary and Laboratory Examination
- Blood count: anaemia identified, and no leucocytosis. Biochemistry: Ca 2.57, AST 0.88, GGT 1.39, LD 4.15, CRP 5.1, other values in the normal range. Tumour markers: CYFRA 21-1 959.6, CA-125 46.4, NSE 221.1.
- T-SPOT negative Mantoux II (Mx II) = 20 mm
- Microbiology of BAL: *Klebsiella pneumoniae*, and *Burkholderia multivorans* positive

Radiology
- *Posteroanterior and lateral chest X-ray*: The lungs are expanded. Multiple diffuse small shadows within the pulmonary parenchyma. Concurrently, obscurations following the course of the lateral ribs bilaterally, interrupting the contour of the VI rib on the right in the lateral course. Overall a slightly heterogeneous bone structure. Vascular markings are adequate. The diaphragm is smooth, with the external angles clear. The cardiac shadow is not increased in size (Fig. 8.45a, b).
- *HRCT of the lungs*: Multiple spherical nodules of various sizes, at most about 12 mm, bilaterally within the pulmonary parenchyma in random distribution. There are also multiple osteolytic lesions affecting the sternum, ribs, and vertebrae. In the left breast, a homogeneous soft-tissue nodule with not smooth edges is found—a left breast tumour (Fig. 8.46a–m).

  Conclusion: Bilateral, multiple small nodules, and in the light of the osteolytic findings may represent a malignancy.

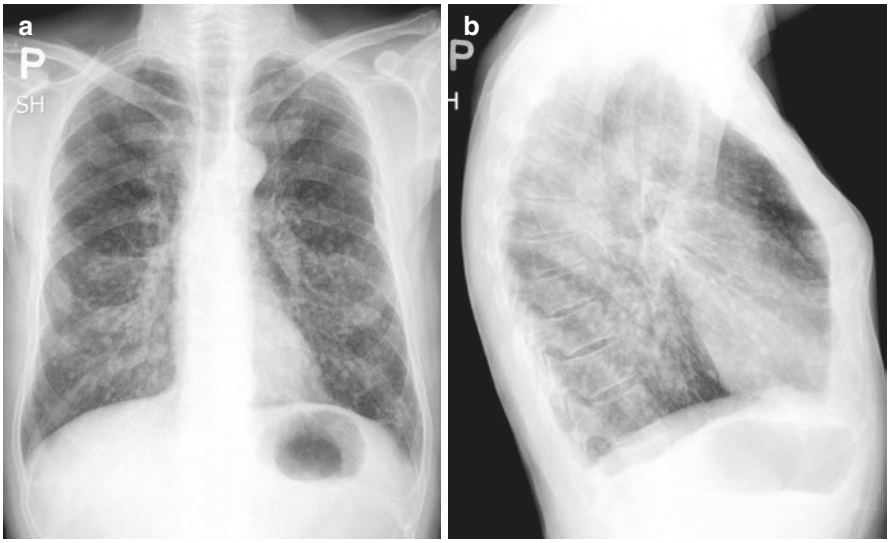

Fig. 8.45 (**a**) Posteroanterior chest X-ray: pulmonary parenchyma with diffuse multiple small shadows. (**b**) Lateral chest X-ray: pulmonary parenchyma with diffuse multiple small shadows

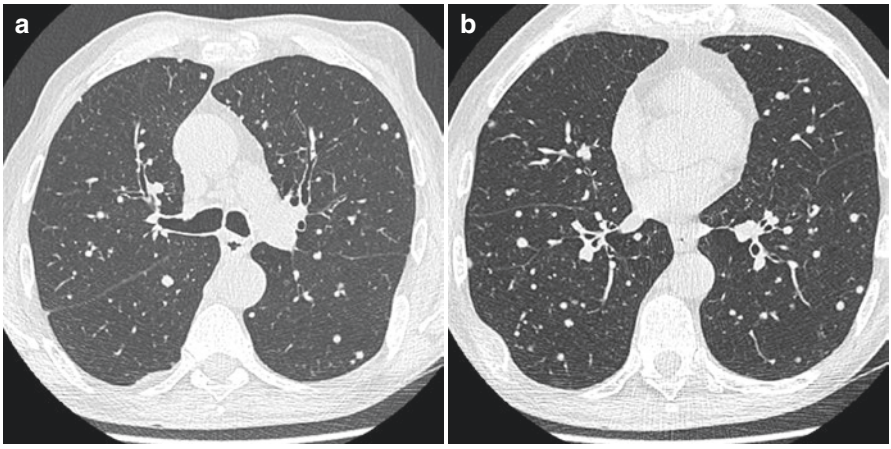

Fig. 8.46 (**a**) HRCT of the lungs: multiple nodules. (**b**) HRCT of the lungs: multiple nodules in both lungs. (**c**) HRCT of the lungs: multiple nodules mainly in dorsal parts of both lungs. (**d**) HRCT of the lungs (coronal reconstruction): multiple nodules, mainly in random distribution. (**e**) HRCT of the lungs (sagittal reconstruction): multiple nodules in a random distribution. (**f**) HRCT of the lungs (MIP reconstruction): multiple nodules. (**g**) HRCT of the lungs (MIP, coronal reconstruction): multiple nodules in a random distribution. (**h**) HRCT of the lungs (MIP, sagittal reconstruction): multiple nodules in a random distribution. (**i**, **j**) HRCT of the lungs (bone window): osteolytic lesion of the rib on the right side. (**k**) HRCT of the lungs (mediastinal window): in the left breast, homogeneous soft-tissue nodule deposit with non-sharp edges—left breast tumour. (**l**) HRCT of the lungs (mediastinal window, coronal reconstruction): in the left breast, homogeneous soft-tissue deposit with non-sharp edges—left breast tumour. (**m**) HRCT of lungs (mediastinal window, sagittal reconstruction): in the left breast, homogeneous soft-tissue deposit with non-sharp edges—left breast tumour

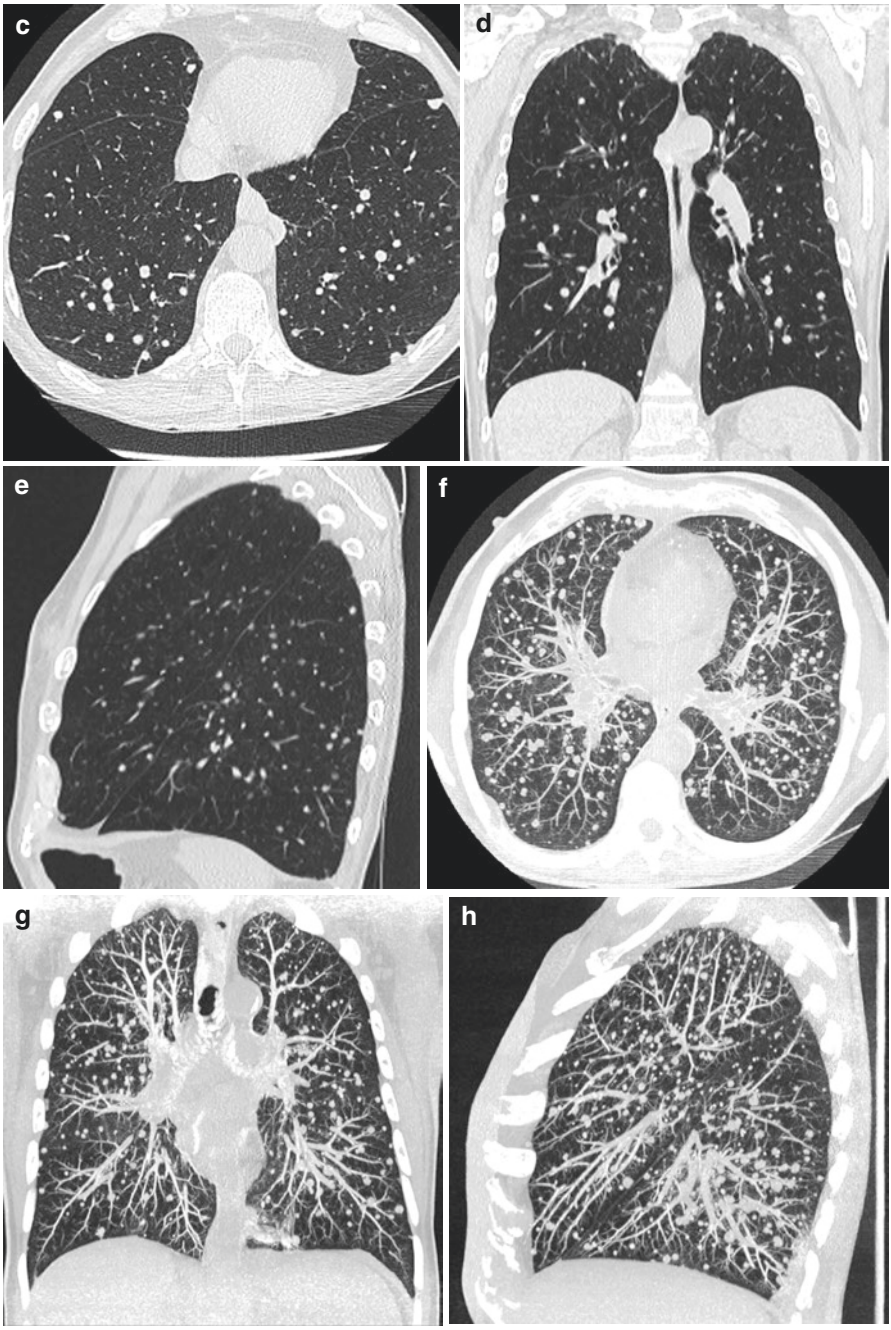

Fig. 8.46 (continued)

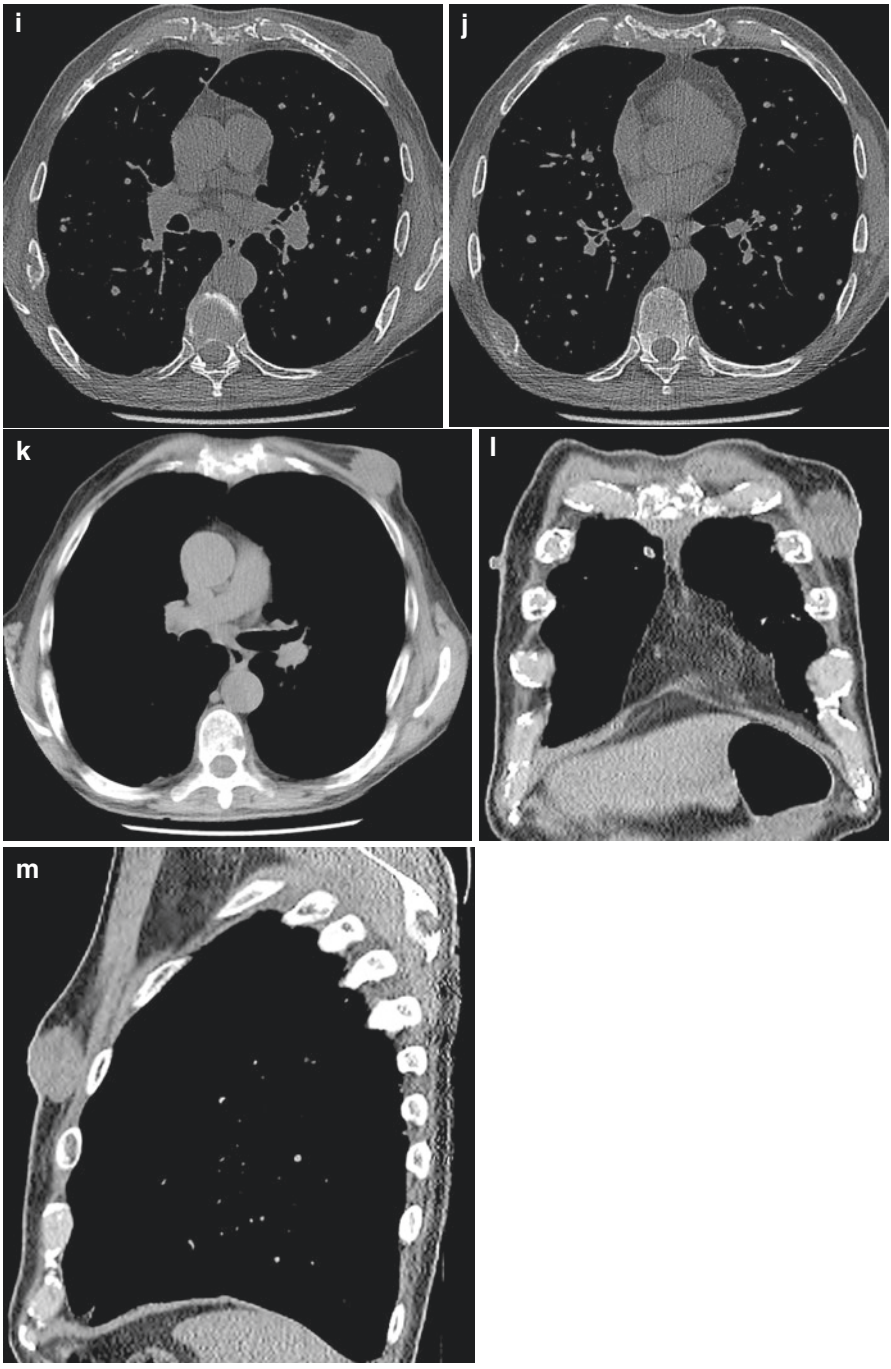

Fig. 8.46 (continued)

Bronchoscopy, Bronchoalveolar Lavage and TBB

- BAL: alveolar macrophages 74%, lymphocytes 24%, neutrophils 2% and eosinophils 0%
- *Conclusion*: Lymphocytic alveolitis, foamy macrophages, and pigmentophages.
- TBB: tumorous changes have not been identified.
- Biopsy of the breast: invasive NST carcinoma (no specific type) ductal G2 (grade 2).

8.9.1 Multidisciplinary Team and Differential Diagnosis

The results were evaluated, and the findings clearly demonstrate metastatic breast cancer (lungs, brain, and bone). A specific disease process is excluded.

8.9.2 Conclusion

A patient with a suspected disease was admitted for examination and treatment. Suspicion was based on clinical and radiological findings, as well as social history. The patient has had no previous treatments. He contacted a physician for the first time in January 2018 for breathing difficulties, and because of a cough, pain, and weight loss. In the autumn of 2016, he found a resistance in the left breast, however, thought this was a lipoma. Subsequently, the patient was examined at our department. An extensive destructive process of the left breast was detected as part of the initial examination, which led to another examination that was focused on the evidence of malignancy. Bronchoscopy with lavage and transbronchial biopsy was performed (without any evidence of tumour changes). Tumour markers CYFRA 21-1, NSE and CA-125 were studied, including a breast biopsy, leading to the evidence of carcinoma and a CT of the brain confirmed evidence of multiple metastases.

Based on the conclusions of the MDT, including a consultation with the oncologist, the patient was transferred to the oncological department for further therapy.

8.9.3 Carcinomatous Lymphangiopathy—What We Should Consider in Differential Diagnosis

1. Sarcoidosis: HRCT—nodules in a perilymphatic distribution—present mainly on the pleura, centrally and peribronchovascularly. The nodules are irregularly distributed, whereby the affection of upper and middle parts of the lungs predominates. Furthermore, enlarged nodes in the mediastinum are usually identified (Fig. 8.47).
2. Silicosis: HRCT—nodules are in a perilymphatic distribution, symmetrically affecting the lungs, predominantly in the upper and middle lung fields. Furthermore, enlarged nodes in the mediastinum with shell-like calcifications are usually identified. This diagnosis is supported by a history of reported occupational exposure to silica dust (Fig. 8.48).

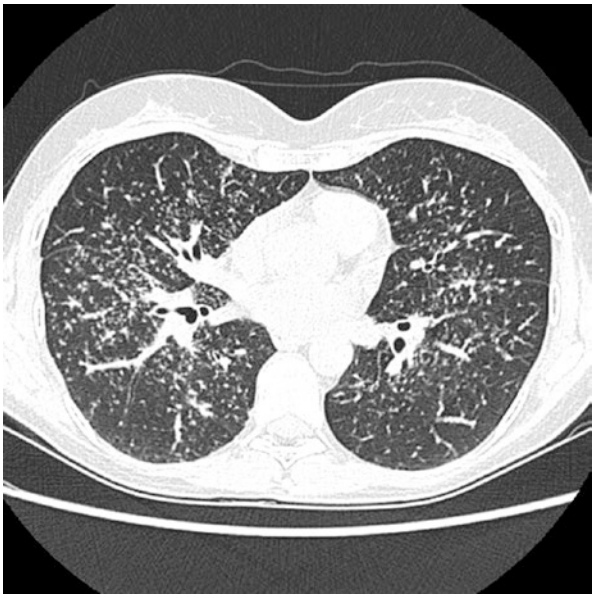

Fig. 8.47 Sarcoidosis: nodules in perilymphatic distribution

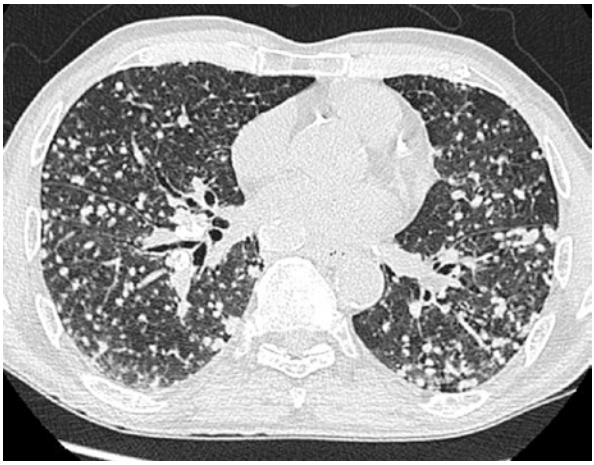

Fig. 8.48 Silicosis: perilymphatic nodules

3. Miliary spread of TB: HRCT—nodules in a random distribution, diffuse, evenly and symmetrically distributed in both lobes. Clinically, severe inflammatory manifestations are present, especially a high fever and profuse sweating (Fig. 8.49).

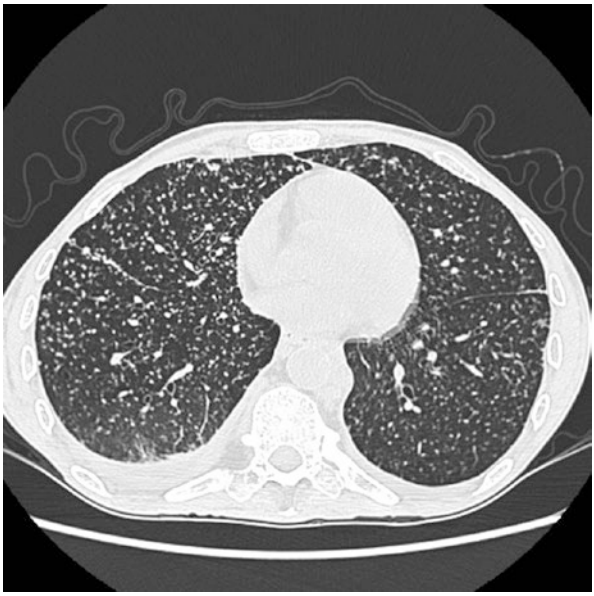

Fig. 8.49 Miliary TB: nodules in random distribution

Further Reading

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High Attenuation Patterns

9

Eva Kocova, Vladimir Bartos, Filip Ctvrtlik, Monika Zurkova, Vladimíra Lostakova, Martina Sterclova, and Jana Votrubova

9.1 Pulmonary Alveolar Proteinosis

Eva Kocova and Vladimir Bartos

Female, 40 years old.

The patient was transferred from a Department of Gynaecology due to an incidental finding on a posteroanterior chest X-ray.

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E. Kocova (ed.), *HRCT in Interstitial Lung Disease*,
https://doi.org/10.1007/978-3-030-16315-0_9

Medical History

- Newly diagnosed microinvasive cervical cancer (staging: T1a1N0M0), otherwise healthy

Occupational History and Exposure

- Weaver (works in a very dusty environment)
- Smoking history: 10 cigarettes a day for 20 years

History of Present Complaint

- The patient had a hysterectomy and pelvic lymphadenectomy due to a microinvasive cervical carcinoma and subjectively experienced postoperative abdominal pain. During the preoperative examination, a random finding of bilateral multiple shadows was noted. Pulmonary symptoms included—a cough, and slight exertional dyspnoea—attributed to smoking.

Objective Finding

- Normal, vesicular breathing, without secondary phenomena.

Examination

Lung Functional Tests

- VC 2.80 L/82% (ref. v), FEV_1 2.12 L/72% (ref. v), Tiff. 72%, TLC 4.14 L/85% (ref. v), RV 1.34 L/83% (ref. v), DL_{CO} 4.29 mmol/L/min/54% (ref. v)
- Mild obstructive ventilatory disorder with a normal vital capacity without pulmonary hyperinflation. A moderately reduced diffuse pulmonary capacity for CO without a restrictive ventilatory disorder

Radiology

- *Posteroanterior chest X-ray*: Bilateral, patch shadows in all lung fields, with a slight predilection basally (Fig. 9.1).
- *HRCT of the lungs*: Bilateral, and especially subpleural, irregular regions of GGO, with smooth and thickened interlobular septa—a crazy paving pattern. There are no nodules, no significant lymphadenopathy, and no signs of fibrosis (Fig. 9.2a–c).

Bronchoscopy with Bronchoalveolar Lavage

- Bronchoscopy was performed and was anatomically normal.
- The BAL fluid was collected and a highly cloudy yellowish fluid was revealed.

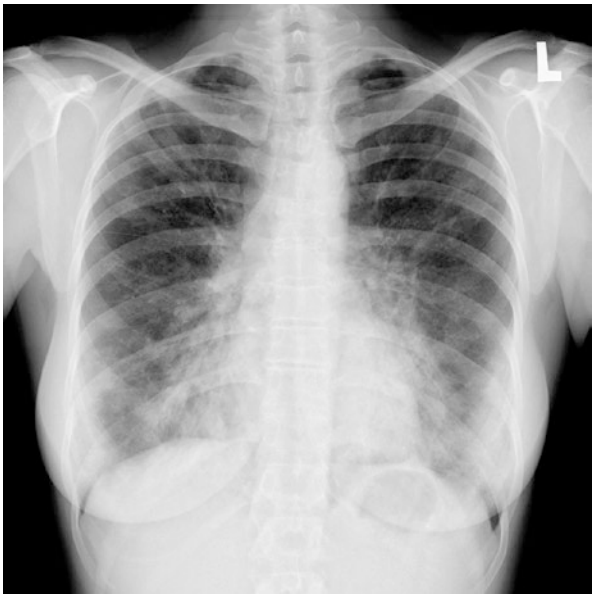


Fig. 9.1 Posteroanterior chest X-ray: bilateral, irregular, hazy, bounded shadows of alveolar nature, with features of an air bronchogram

Auxiliary and Laboratory Examination

- A full blood count and biochemical studies were physiological. Rheumatological screening reveals no abnormalities, and there is no evidence of immunodeficiency. Examination of autoantibodies against granulocyte and macrophage growth factor (GM-CSF) was not performed (unavailable).

9.1.1 Multidisciplinary Team and Differential Diagnosis

According to HRCT—crazy paving patterns—in the differential diagnosis, an infection caused by an atypical agent should be especially considered. Also, pulmonary alveolar proteinosis (PAP), alveolar haemorrhage and adenocarcinoma with lepidic growth are considered. SCTD was excluded by the rheumatologist.

According to the BAL analysis by the pathologist, signs of alveolar proteinosis are present (PAS positive material). An infectious aetiology of the findings was excluded (serologically and by examination of the BALF).

The conclusion of the MDT: According to the clinical, radiological, and pathological reasoning, this is a representation of alveolar proteinosis. It is recommended to perform a targeted therapeutic bronchoscopic lavage of the left lung, and of the right lung after a delay. Due to the patient's fear of cancer, and the finding of rare atypical cells in the BAL, a histological verification was performed with VATS, confirming PAP and eliminating malignancy.

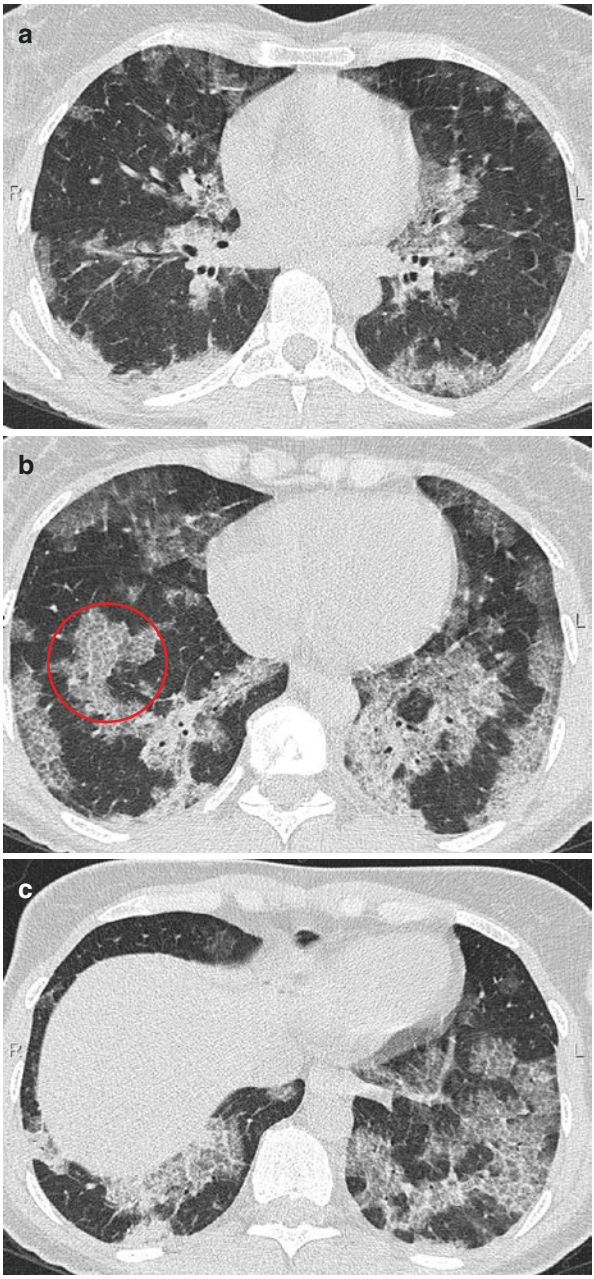


Fig. 9.2 (**a**) HRCT of the lungs: patchy areas of GGO. (**b**) HRCT of the lungs: GGO and smooth thickened interlobular septa—crazy paving. (**c**) HRCT of the lungs: GGO and smoothly thickened interlobular septa with predilection subpleurally

Therapeutic Bronchoalveolar Lavage

- 16 L of normal saline solution were instilled on the left, withdrawing 16 L. After the procedure, which was without complication, the patient had no respiratory insufficiency.
- Four months later, the lavage was performed on the right—instilled 16 L of normal saline solution, withdrawing 15 L. After the procedure, the patient remained without complications.
- During both procedures, the normal saline solution was warmed to body temperature, in fractions of 500–1000 mL. The drained fluid was initially yellowish, gradually becoming clearer, with the last samples being completely clear.

9.1.2 Conclusion

The radiological patterns of alveolar proteinosis were confirmed by the BAL and histologically. After reviewing the control HRCT of the lung, there was a significant regression of crazy paving patterns after bilateral therapeutic lavage (Fig. 9.3). A plain chest X-ray and HRCT of the lungs 7 years later revealed normal findings. After the diagnosis, the patient stopped smoking (other treatment was not indicated), and is now asymptomatic with normal pulmonary function, except for a slight reduction in pulmonary diffusion for CO.

9.1.3 Pulmonary Alveolar Proteinosis

Combinations of clinical, radiological and pathological investigations are required to determine the diagnosis of pulmonary alveolar proteinosis.

The radiological scans with the typical pattern of crazy paving—a combination of GGO and smooth thickened interlobular septa. Typically, it is patchy, with a slight predilection basally.

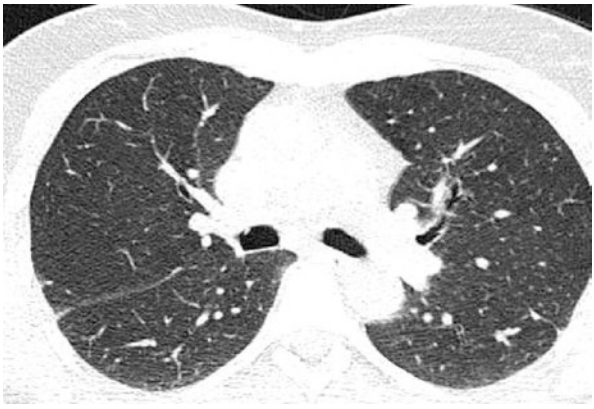


Fig. 9.3 Repeated HRCT of the lungs after seven year: nearly normal finding, only small areas of GGO bilaterally

However, this finding is not specifically characteristic only of alveolar proteinosis, and other causes of crazy paving (especially infections) must be clinically and pathologically excluded.

An essential part of the diagnosis is the BAL, which is later also a therapeutic instrument.

Note

- The diagnosis of pulmonary alveolar proteinosis is a combination of clinical, radiological, and pathological examinations. The crazy paving pattern on the lung HRCT may be due to infections, with atypical agents (*Mycoplasma pneumoniae*, *Pneumocystis jirovecii*), alveolar haemorrhage, alveolar proteinosis, ARDS, lung malignancies, etc.
- In alveolar proteinosis, the pattern of crazy paving can be either extensively or only slightly indicated.

9.1.4 Pulmonary Alveolar Proteinosis—What We Should Consider in Differential Diagnosis

1. ARDS: This patient lacks an inducing cause, and, in particular, the clinical condition does not match the diagnosis of alveolar proteinosis (Fig. 9.4).
2. Pulmonary infection/pneumonia: Especially Mycoplasma pneumoniae, and Pneumocystis carinii, viral—excluded by BAL (Fig. 9.5).
3. Diffuse alveolar haemorrhage: Excluded by BAL (Fig. 9.6).

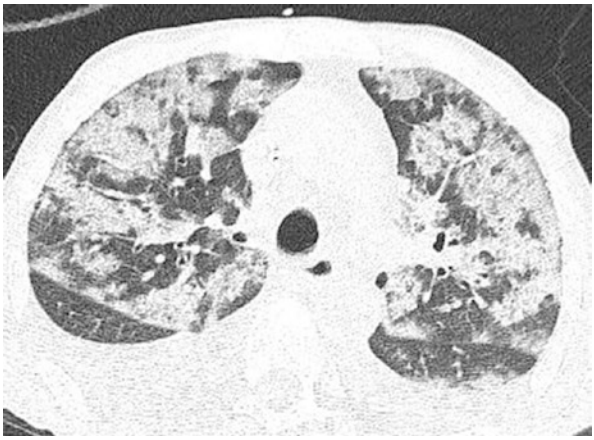


Fig. 9.4 ARDS: bilateral consolidations

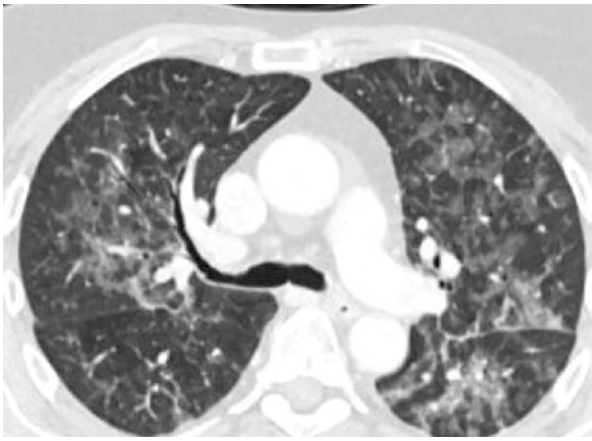


Fig. 9.5 Infection: bilateral patchy areas of GGO

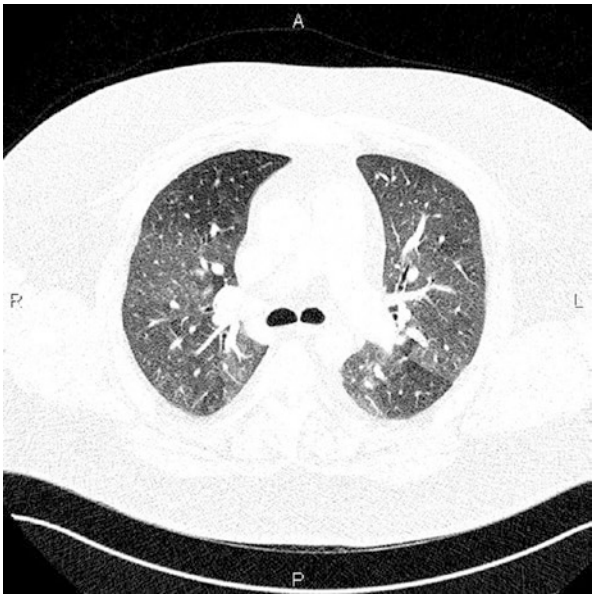


Fig. 9.6 Diffuse alveolar haemorrhage: diffuse GGO

4. Organising pneumonia (OP): Typical shred-like consolidations of the pulmonary parenchyma, peripherally, peribronchially, with air bronchogram (Fig. 9.7).
5. Adenocarcioma with lepidic growth: Mostly patchy GGO or minor consolidations, with air bronchogram, including mediastinal and hilar lymphadenopathy (Fig. 9.8).

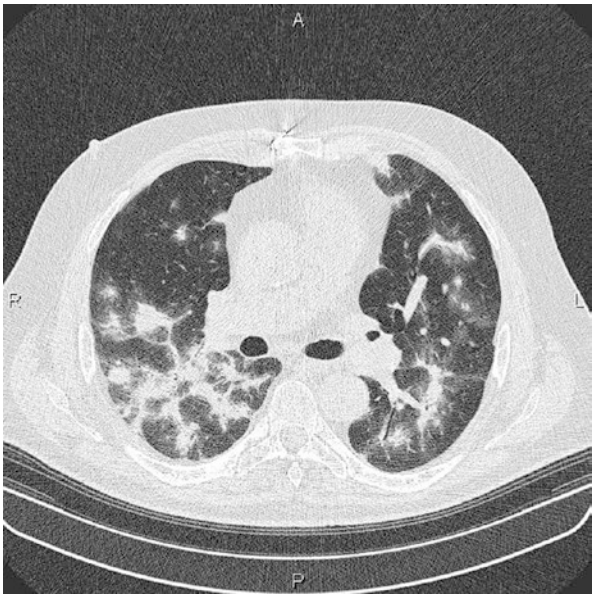


Fig. 9.7 Organising pneumonia: band-like consolidations

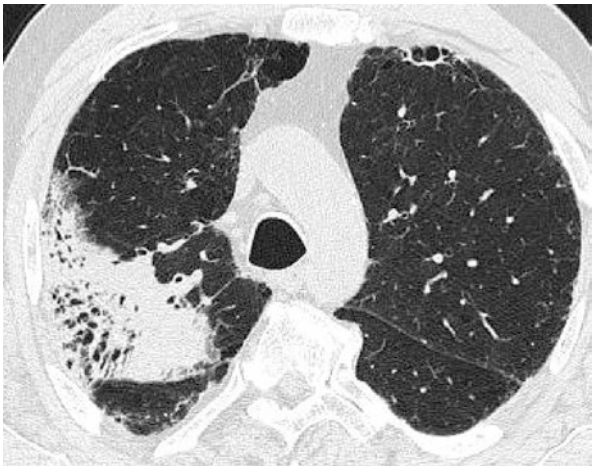


Fig. 9.8 Adenocarcinoma with lepidic growth: consolidation with air bronchogram

9.2 Drug-Induced Lung Disease—Amiodarone

Eva Kocova and Vladimir Bartos

Male, 77 years old.

Patient with severe cardiac disease and on long-term treatment for chronic obstructive pulmonary disease, presenting with an unclear finding of new peripheral consolidations incidentally captured on CT aortography.

Medical History

- Chronic obstructive pulmonary disease stage 2–3—chronic bronchitis, centrilobular pulmonary emphysema, and frequent exacerbations
- Atrial fibrillation—on long-term warfarin, ICD implantation (implantable cardioverter-defibrillator), heart failure, left ventricular ejection fraction (LVEF) 20%, and significant tricuspid insufficiency
- IHD, previous myocardial infarction, aortocoronary bypass and repeated stenting of the coronary arteries
- Radical resection of the rectosigmoid colon due to carcinoma, with no evidence of recurrence or dissemination, and no other oncological treatment
- Medication history: polypragmasia including amiodarone use for 4 years 200 mg daily

Occupational History and Exposure

- Pensioner, formerly a technical clerk, worked in a clean environment
- Lives with his son, without pets
- Smoking history: ex-smoker, used to smoke 20 cigarettes a day for 25 years

History of Present Complaint

- He has had exertional dyspnoea for years, which has been aggravated over recent weeks. Has received repeated antibiotic therapy, which has been without any beneficial effect. He expectorates white phlegm, is apyrexial, and is maintaining his weight.

Objective Finding

- Vesicular breathing, rare bilateral rales—especially basally. A pacemaker is in situ in the area below the clavicle, otherwise, findings are normal.

Examination

Lung Functional Tests

- VC 2.24 L/63% (ref. v), FEV_1 1.57 L/59% (ref. v), Tiff. 65%, MEF50 1.34 L/36% (ref. v), RV 2.91 L/108% (ref. v), TLC 5.30 L/81% (ref. v), RV/TLC 55%, DL_{CO} 3.65/46% (ref. v), K_{CO} 0.93/77% (ref. v)
- Moderate obstructive pulmonary disease, with a slight decrease in vital capacity and pulmonary hyperinflation. There is a moderately decreased pulmonary diffusion for CO

Radiology

- *CT aortogram*: Thickened interlobular septa, GGO, and mild bilateral consolidations subpleurally in the lower lobes of the lungs (Fig. 9.9).

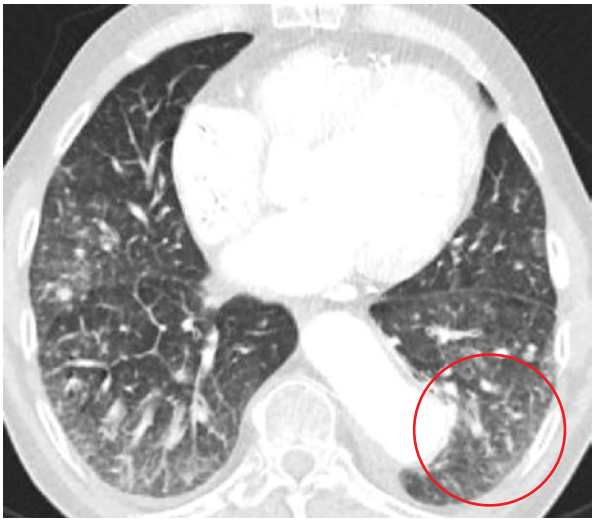


Fig. 9.9 CT of aorta: bilateral and basal GGO

- *HRCT of the lungs*: Findings of centrilobular pulmonary emphysema, multiple dispersed regions of GGO and consolidations. Smooth thickened interlobular septa, especially basally, and a small fluidothorax is identified on the right. The liver parenchyma contains localised densities up to 80 HU (Fig. 9.10a–d).

9.2.1 Multidisciplinary Team and Differential Diagnosis

Advanced centrilobular emphysema, GGO and minor consolidations (consolidations are increasingly dense—around 35 HU), and smooth thickened interlobular septa are seen predominantly in basal zones. Additionally, cardiomegaly, significant calcification of the coronary arteries, mediastinal lymphadenopathy, and minimal fluidothorax on the right are identified. The hepatic parenchyma captured marginal densities up to 80 HU. According to the HRCT, it is first necessary to consider amiodarone-induced pulmonary disease in the differential diagnosis. It is also advisable to exclude pulmonary infection, heart failure, and adenocarcinoma with lepidic growth.

Amiodarone withdrawal and BAL are recommended. A TBB is not indicated due to multiple co-morbidities, the poor overall condition of the patient (PS 2–3) and due to the rejection of possible oncological treatment by the patient.

The conclusion of the MDT: Clinically and radiologically, it is probably an amiodarone-induced pulmonary disease. Amiodarone withdrawal and bronchoalveolar lavage are recommended.

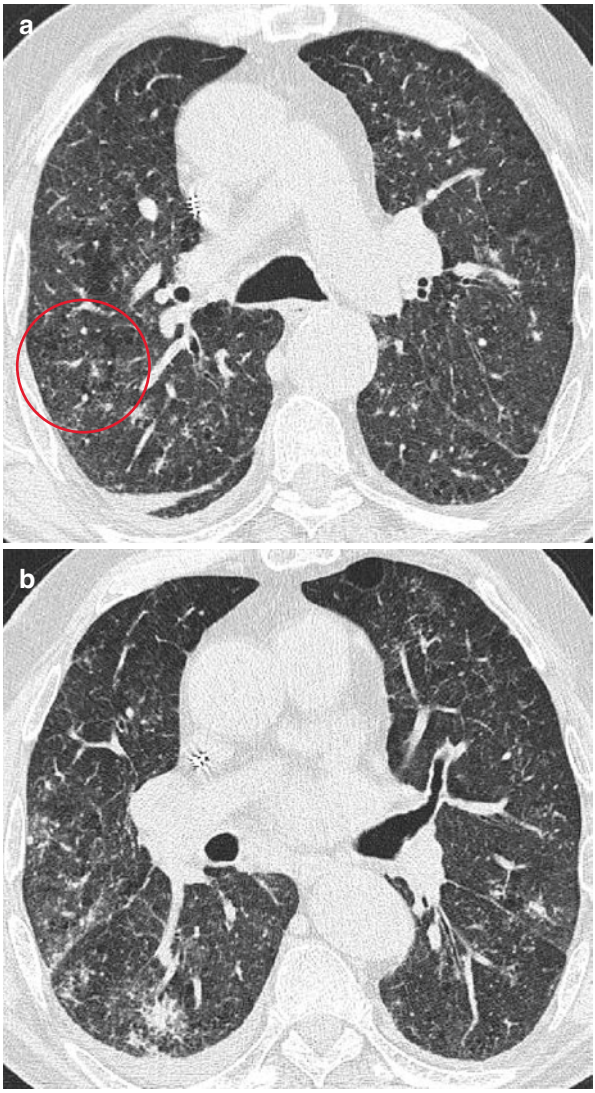


Fig. 9.10 (**a**) HRCT of the lungs: centrilobular pulmonary emphysema, diffuse reticulations. (**b**) HRCT of the lungs: centrilobular pulmonary emphysema, GGO and patchy consolidations. (**c**) HRCT of the lungs: GGO and consolidations, consolidations are with high density (density of the liver parenchyma). (**d**) CT of the liver (soft tissues window): high diffuse density of the liver parenchyma

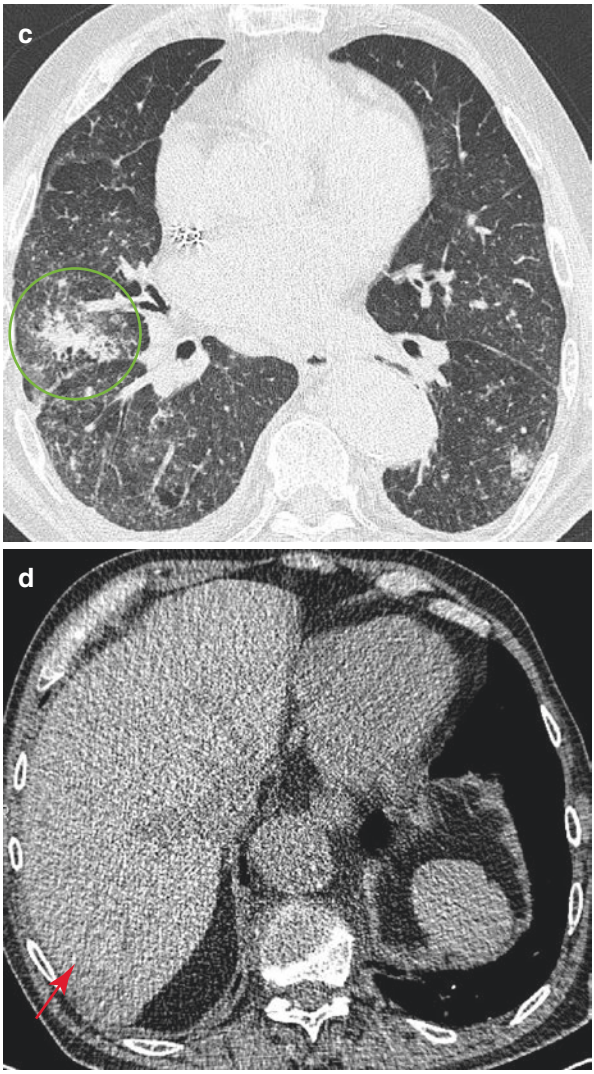


Fig. 9.10 (continued)

Bronchoscopy with Bronchoalveolar Lavage

- 92% alveolar macrophages, mostly macrophages with fine foamy cytoplasm, 2% lymphocytes, 6% neutrophils, and no malignant cells. There is no evidence of infection, including opportunistic infections.
- The finding of foamy macrophages supports the diagnosis of an amiodarone-induced lung disease.

9.2.2 Conclusion

The findings were concluded as an amiodarone-induced lung disease on a background of pulmonary emphysema and heart failure. After amiodarone withdrawal, there was a regression of the findings on a chest X-ray, and corticosteroid therapy was not indicated.

Note

- Many current commonly used drugs have a pneumotoxic effect.
- To determine the diagnosis of a drug-induced pulmonary disease, the knowledge of the pharmacological history is essential. A diagnosis is usually determined by exclusion, i.e. it is always necessary to rule out other causes.
- An overview of drug pneumotoxicity is illustrated on www.pneumotox.com.

9.2.3 Drug-Induced Lung Disease—What We Should Consider in Differential Diagnosis

1. Cryptogenic organising pneumonia: Shred-like consolidations—differential diagnostics based only on the radiological image are very difficult—in amiodarone-induced lung disorders, the consolidation has a higher density, and an increased density within the liver parenchyma (Fig. 9.11).
2. Eosinophilic pneumonia: GGO, rather in the upper lobes, peripherally, with a typical finding in the bronchoalveolar fluid (Fig. 9.12).
3. Organising pneumonia in systemic connective tissue disease (consolidations may be migratory) (Fig. 9.13a, b).
4. Adenocarcinoma with lepidic growth: Histological verification is required (Fig. 9.14).

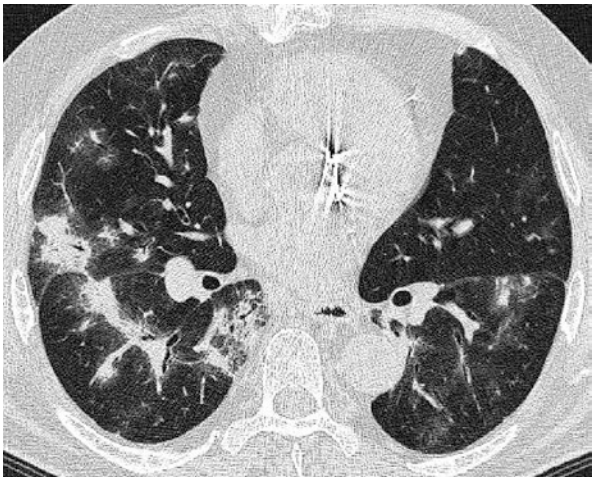


Fig. 9.11 Organising pneumonia: strip-like consolidations

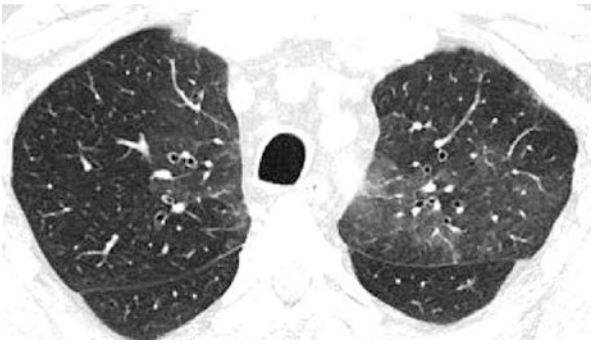


Fig. 9.12 Eosinophilic pneumonia: areas of GGO

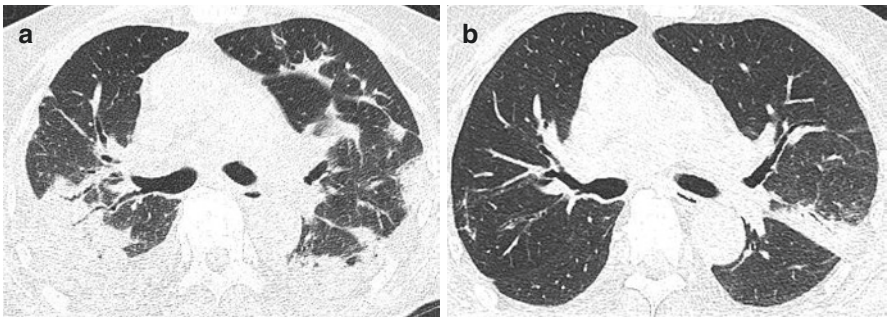


Fig. 9.13 (**a**) Organising pneumonia in systemic connective tissue disease: a CT scan from 5/2015 multiple consolidations of the pulmonary parenchyma bilaterally and peripherally. (**b**) Organising pneumonia in systemic connective tissue disease the same patient as previous scan: CT scan from 2/2016: clear regression of previously apparent consolidations, with new consolidations in the left upper lobe located by the interlobar fissure

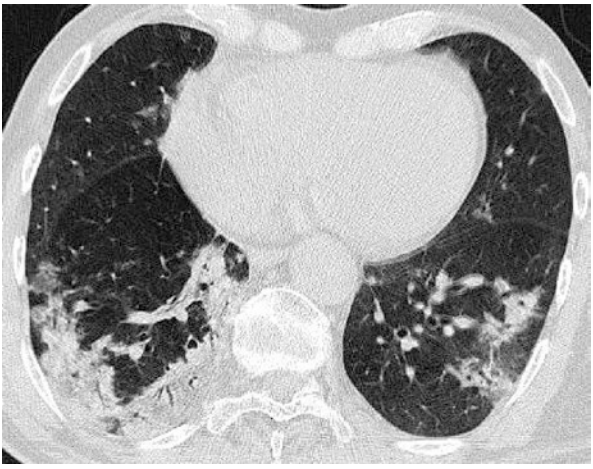


Fig. 9.14 Adenocarcinoma with lepidic growth: bilateral GGO and areas of consolidations

9.3 Cryptogenic Organising Pneumonia

Eva Kocova and Vladimir Bartos

Male, 68 years old.

Admitted to finalise examinations for persisting lung consolidations after pneumonia.

Medical History

- Type 2 diabetes mellitus
- Atrial fibrillation—on anticoagulant therapy

Occupational History and Exposure

- Pensioner (for 6 years), previously worked as an electrician
- Lives in a block of flats
- Smoking history: non-smoker

History of Present Complaint

- He was treated with antibiotics for right-sided community-acquired pneumonia (he had an elevated body temperature, cough, and worsening dyspnoea) 2 months ago. Even after ATB treatment, he has symptoms of fatigue, night sweats, with a prevalent dry tickling cough. He was no longer feverish and or short of breath.

Objective Finding

- Vesicular breathing, rare basal rales—more on the left side, and resonant lung percussion.

Examination

Lung Functional Tests

- VC 2.79 L/64% (ref. v), FEV_1 1.96 L/59% (ref. v), Tiff. 66%, RV 2.59 L/97% (ref. v), TLC 5.46 L/74% (ref. v), DL_{CO} 7.12/78% (ref. v), K_{CO} 1.43/122% (ref. v)
- A mild combined ventilatory disorder, transfer factor for CO slightly reduced

Radiology

- *HRCT of the lungs*: Multiple regions of GGO and consolidations (Fig. 9.15a–d).

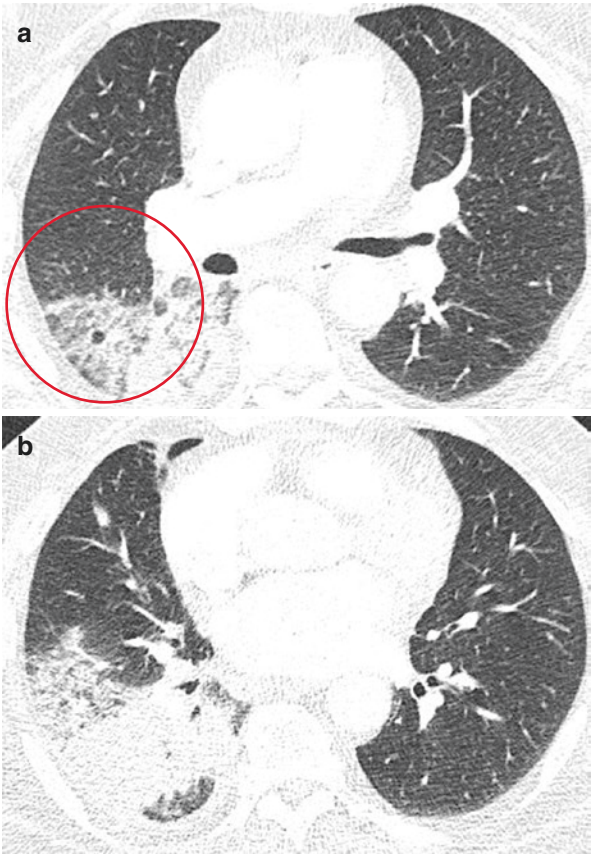


Fig. 9.15 (**a**, **b**) HRCT of the lungs: region of GGO and consolidation in the right lung. (**c**) HRCT of the lungs: bilateral consolidations. (**d**) HRCT of the lungs: bilateral consolidations with GGO in the periphery of consolidations

9.3.1 Multidisciplinary Team and Differential Diagnosis

Persistent localised consolidations, with a newly identified pathology on the left. Laboratory investigations reveal only a slight increase in inflammatory markers.

It is recommended to perform a BAL with TBLB.

The conclusion of the MDT: Clinically and radiologically, it is probably an infectious aetiology of consolidations.

Bronchoscopy, Bronchoalveolar Lavage and TBB

- Normal endobronchial finding.
- The BAL fluid contains 42% alveolar macrophages, 46% lymphocytes with a slight predominance of CD4+, 5% neutrophils, 5% eosinophils, 2% mast cells, and malignant cells not found. Microbiological findings are negative.
- TBB: The finding is characteristic of interstitial pneumonia with features of organising pneumonia. Malignant structures are not found.

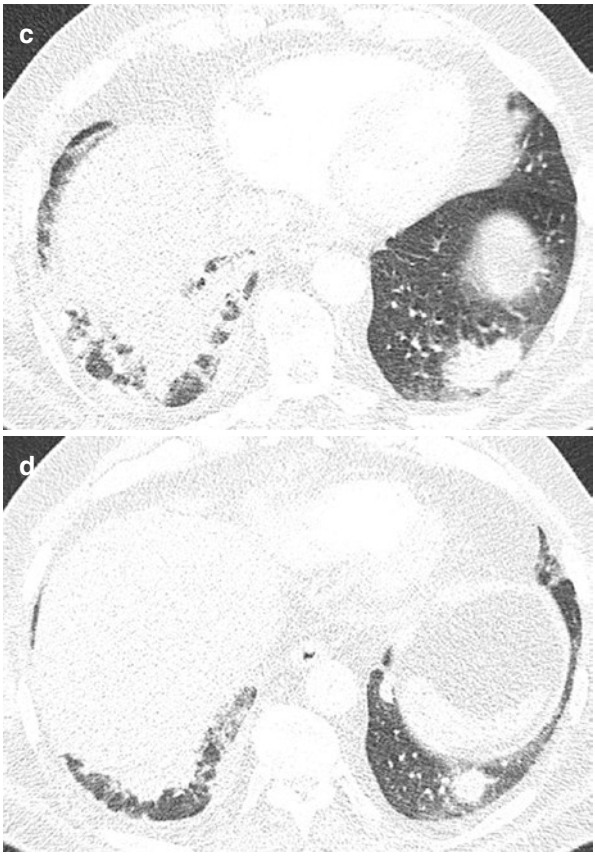


Fig. 9.15 (continued)

Auxiliary and Laboratory Examinations

- Blood count and differential count are normal, without eosinophilia.
- Rheumatological screening is negative, and there is no evidence of immunodeficiency.

9.3.2 Conclusion

Broad-spectrum antibiotic therapy was initiated but without any clinical improvement. The findings were concluded as cryptogenic organising pneumonia—Corticosteroid therapy was initiated, which had a beneficial and rapid clinical effect, with regression of the findings on a chest X-ray. Laboratory markers of inflammation also decreased. After a year, the corticosteroid therapy was withdrawn, as the

patient was asymptomatic and the findings on a plain chest X-ray were normalised. However, during the next consultation, the patient's symptoms reoccurred. A further HRCT of lungs revealed evidence of multiple peribronchial consolidations and GGO, with no necrosis apparent; however, a minor fluidothorax was identified on the left (Fig. 9.16). A BAL was performed, in which the fluid was without evidence of infection. This was assessed as a relapse of the disease, and corticosteroid therapy was re-initiated with a good effect.

Note

Cryptogenic organising pneumonia on HRCT is characterised particularly by regions of consolidations, typically shred-like, subpleurally and peribronchovascularly, often forming nodules to masses with smooth borders. The described "Atoll sign" or "reverse halo sign" is referred to as a very specific sign of this disease (Fig. 9.17).

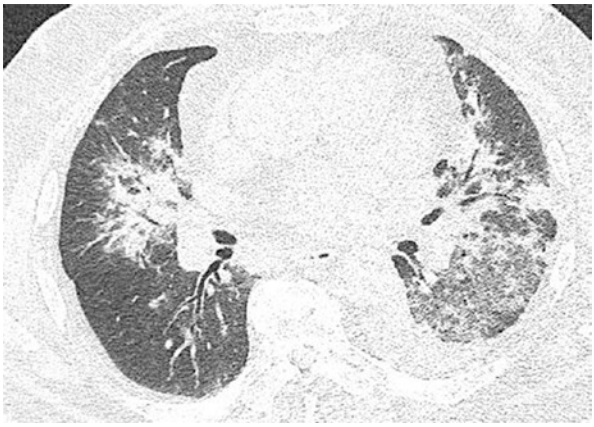


Fig. 9.16 Repeat HRCT of the lungs: multiple peribronchial consolidations and GGO, and a minor fluidothorax on the left

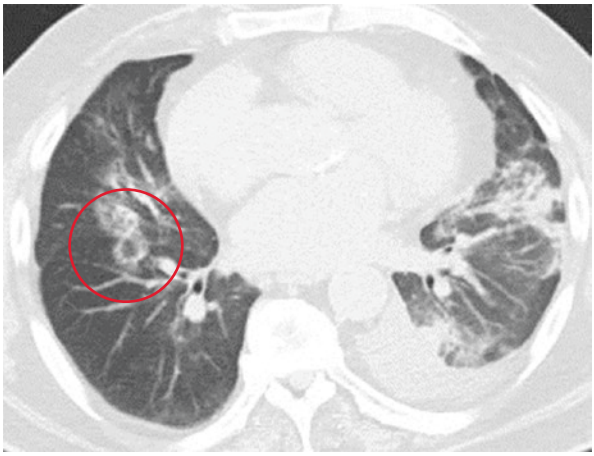


Fig. 9.17 HRCT of the lung: Atoll sign—GGO surrounded with consolidation

9.3.3 Cryptogenic Organising Pneumonia—What We Should Consider in Differential Diagnosis

1. Chronic eosinophilic pneumonia: Homogeneous consolidations with a preserved air bronchogram subpleurally (Fig. 9.18).
2. Vasculitis: Irregularly bounded consolidations peribronchovascularly, and GGO. The consolidations may be migratory (Fig. 9.19).
3. Adenocarcinoma with lepidic growth: Smoothly bounded nodules, consolidations with air bronchogram, and regions of GGO—histological verification required (Fig. 9.20).
4. Pulmonary infarct with pulmonary embolism: Defects in the contrast medium are displayed in the pulmonary arteries within a CT pulmonary angiogram, with typical wedge shape consolidations with the wide bases attached subpleurally, and GGO centrally (Fig. 9.21).

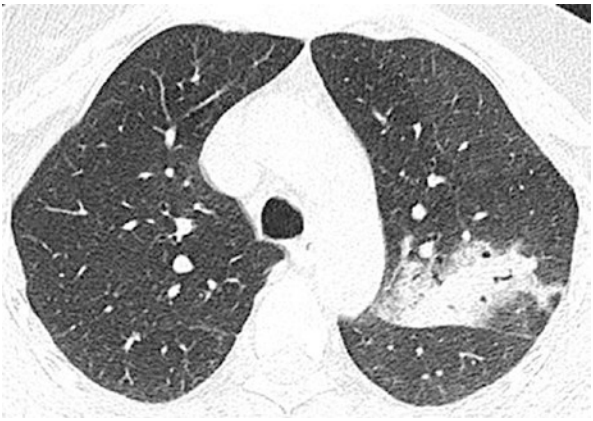


Fig. 9.18 Chronic eosinophilic pneumonia: consolidations with air bronchogram

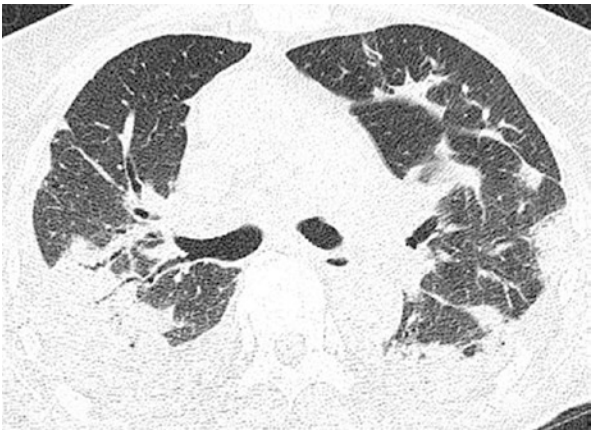


Fig. 9.19 Vasculitis: bilateral consolidations and GGO

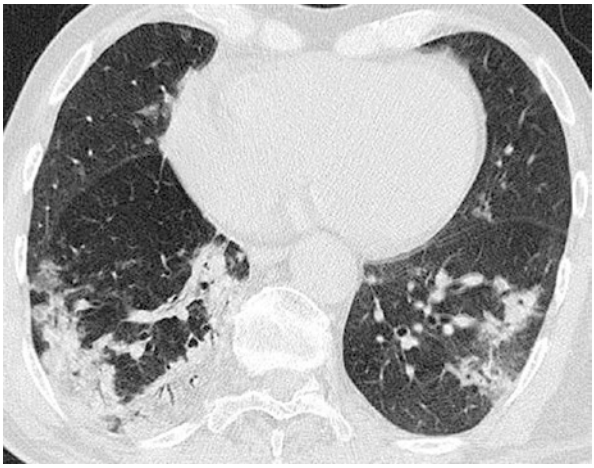


Fig. 9.20 Adenocarcinoma with lepidic growth: Consolidations with air bronchogram

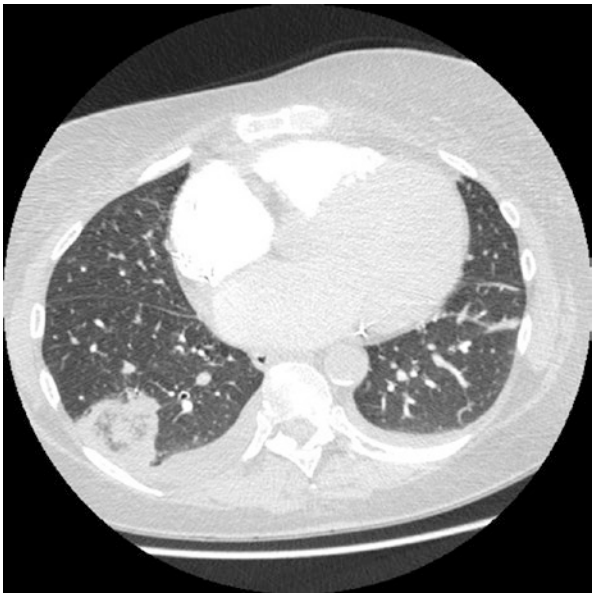


Fig. 9.21 Pulmonary infarct with pulmonary embolism: wedge shape consolidations with the wide bases attached subpleurally, and GGO centrally

9.4 Eosinophilic Granulomatosis with Polyangiitis

Filip Ctvrtlik, Monika Zurkova, and Vladimira Lostakova

Male, 50 years old.

Patient referred by a corresponding internal medicine department due to acute changes identified on HRCT of the chest, pericardial effusion, neuropathy of the lower limbs and concurrent asthma.

Medical History

- Asthma, arterial hypertension, dyslipidaemia, hyperuricaemia. History of left renal colic, appendectomy, bilateral nose polypectomy, Perthes disease, vertebrogenic algic syndrome, and carpal tunnel syndrome

Occupational History and Exposure

- The manager of a meat production company
- Smoking history: non-smoker

History of Present Complaint

- During patient stay in small community hospital, a CT angiogram was performed to exclude pulmonary artery embolism. Numerous enlarged lymph nodes in the mediastinum were found, and in the pulmonary parenchyma, irregular thickening of interlobar fissures and peribronchovascular interstitium was identified with pleural and pericardial effusion. Subsequently, a chest HRCT was completed, where interstitial changes were found bilaterally with predominance in the lower lobes. Further examinations at Department of Respiratory Medicine are required.

Objective Finding

- Vesicular breathing and slight basal crepitations.

Examination

Lung Functional Tests

- VC 5.17 L/102% (ref. v), FEV_1 3.83 L/98% (ref. v), TI% VC_{max} 74%, MEF25 47%, TLC 124%.
- Borderline mild obstructive ventilatory disorder, TLC in range, moderate RV elevation, mild pulmonary hyperinflation, and slight airway resistance.
- DL_{CO}sb: DL_{CO} 84%, K_{CO} 81%.
- Transfer factor and transfer coefficient are normal.

Auxiliary and Laboratory Examinations

- ANCA—negative.
- Cardiology investigations: the effusion is assessed as primarily non-cardiac.
- Kidney Function: normal.
- Neurological examination: algodysesthesia of soles of the feet, gait abnormality, and symmetric L5/S1 hyporeflexia without lower limb paralysis.

Aetiology: A very suspicious distal and symmetric polyneuropathy, this represents a manifestation of an unknown underlying disease.

Radiology

- *Anterior-posterior and lateral chest X-ray*: Basal strip-like shadows and reticulations in the mid-zone and lower pulmonary fields.
- *HRCT of the lungs*: Bilateral irregular non-segmental regions of GGO and consolidations predominating peripherally. Concurrently, a bilateral interlobular septa thickening is apparent. Basally, there is pronounced diffuse thickening of the bronchial walls and pulmonary artery enlargement. On the right, there is mild pleural fluid, and nodules present only rarely (Fig. 9.22a–h).

Bronchoscopy, Bronchoalveolar Lavage and TBB

- *BAL*: Lymphocytic (16%) and eosinophilic (27%) alveolitis. Numerous erythrocytes in the background.
- *TBB*: Vasculitis without granulomas, without fibrinoid necrosis, however with significant eosinophilic infiltration. In the surrounding pulmonary tissue, there is organising pneumonia. In the differential diagnosis, we consider eosinophilic pneumonia or vasculitis with eosinophilia, and the findings are supported by a clinical suspicion of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

9.4.1 Multidisciplinary Team and Differential Diagnosis

The patient meets the diagnostic criteria for eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) on the basis of the HRCT image, histological verification from the TBLB and BAL cytology. Additionally, there is evidence of neurological and cardiac impairment.

9.4.2 Conclusion

Findings are concluded as eosinophilic granulomatosis with polyangiitis, and the patient was indicated for pulse corticosteroid therapy, followed by the transition to oral prednisone, at a dose of 50 mg/day, reducing the dose gradually.

Note

- When bilateral HRCT findings of multiple irregular regions of consolidations in the presence of chronic symptoms are found, consider organising pneumonia and chronic eosinophilic pneumonia.
- With concurrent bronchial asthma, it may also be the rarer Churg-Strauss syndrome (EGPA).
- In wider differential diagnosis, in patients with chronic bilateral consolidations, it is also important to remember adenocarcinoma with lepidic growth or lymphoma.

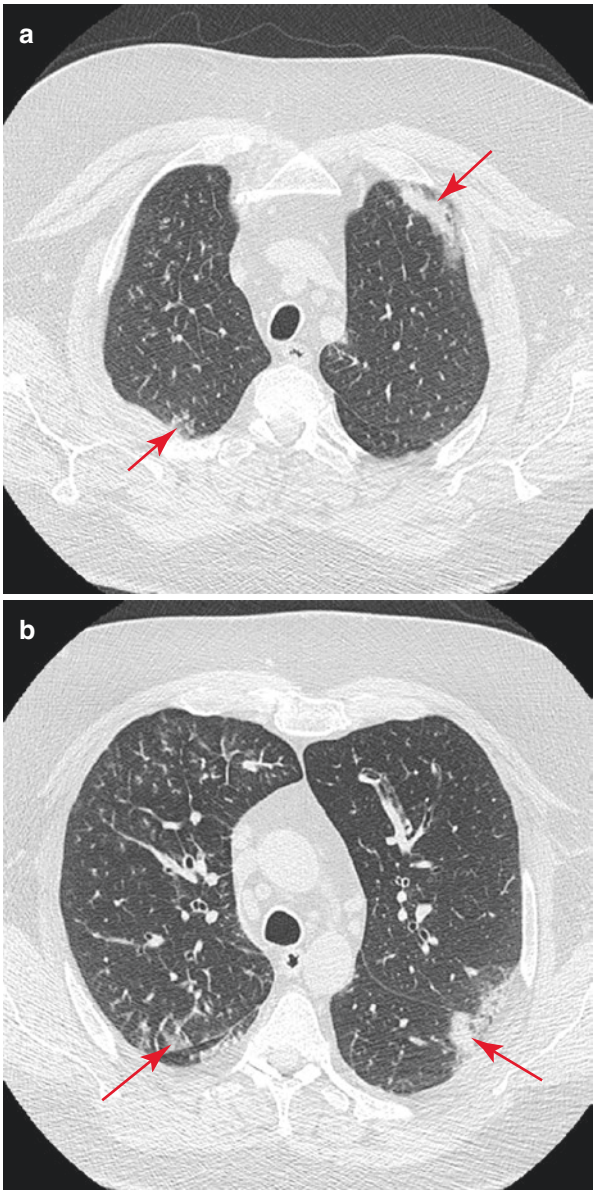
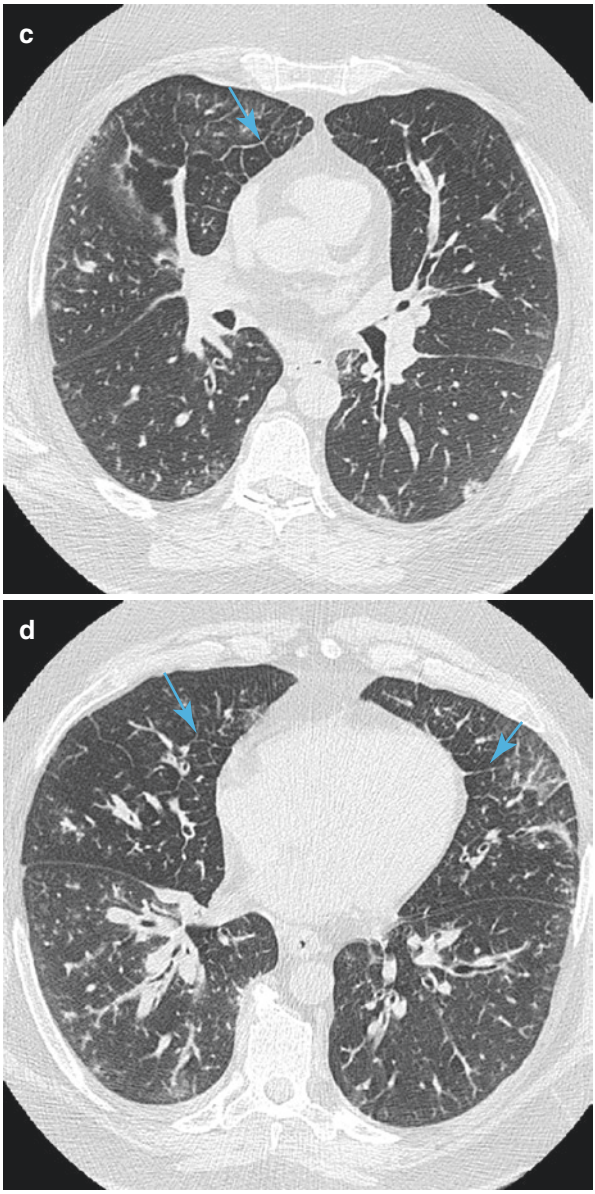


Fig. 9.22 (**a**) HRCT of the lungs: regions of GGO and consolidations predominating in the periphery of the lungs. (**b**) HRCT of the lungs: GGO and consolidations subpleurally. (**c**) HRCT of the lungs: bilateral thickening of the interlobular septa. (**d**) HRCT of the lungs: bilateral thickening of the interlobular septa and patchy areas of GGO. (**e**) HRCT of the lungs: thickening of the bronchial walls and enlargement of the pulmonary arteries bilaterally. (**f**) HRCT of the lungs: thickening of the bronchial walls. (**g**) HRCT of the lungs (coronal reconstruction): thickening of the bronchial walls and enlargement of the pulmonary arteries, GGO and consolidations in the periphery of the lungs. (**h**) HRCT of the lungs (coronal reconstruction): thickening of interlobular septa



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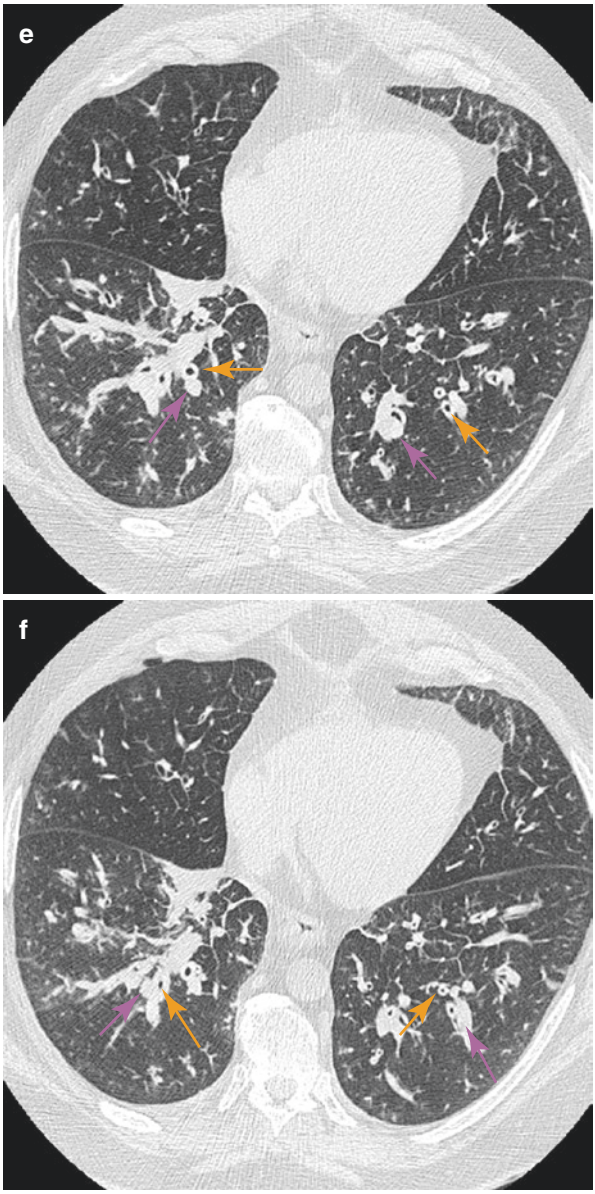

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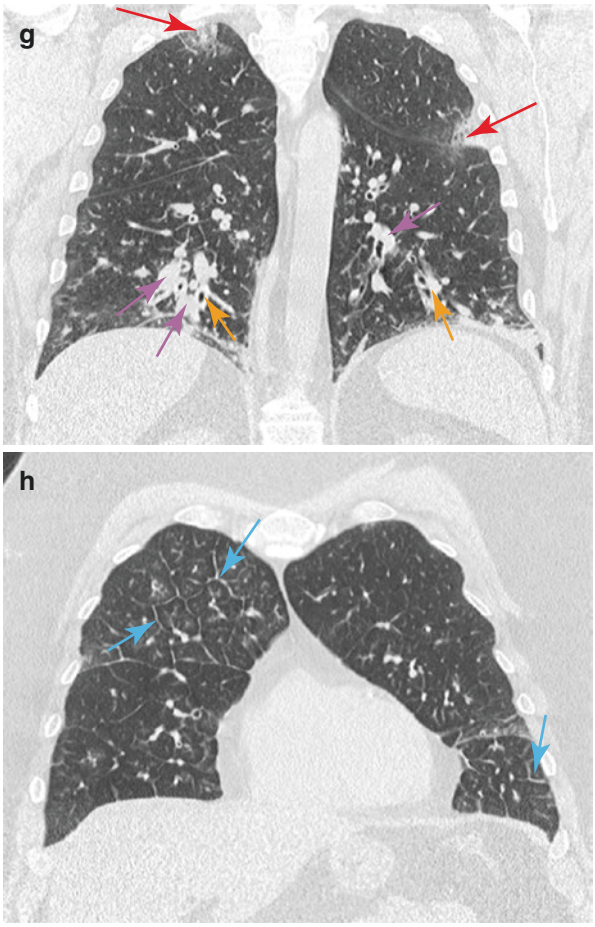

Fig. 9.22 (continued)

9.4.3 Eosinophilic Granulomatosis with Polyangiitis—What We Should Consider in Differential Diagnosis

1. Chronic eosinophilic pneumonia: bilateral multiple irregular regions of consolidation (GGO) in the periphery of the lungs, even peribronchovascularly. Unlike organising pneumonia, the pathology may also prevail cranially, although this cannot always be distinguished with HRCT alone. Clinically, 50% of the patients have asthma (Fig. 9.23).
2. Organising pneumonia: HRCT—bilateral multiple irregular regions of consolidations (GGO) in the periphery of the lobes or peribronchovascularly. It often creates a sign of bilateral multiple bizarre nodules. It can predominate caudally, and on occasion the "Atoll sign" is present (Fig. 9.24a, b).

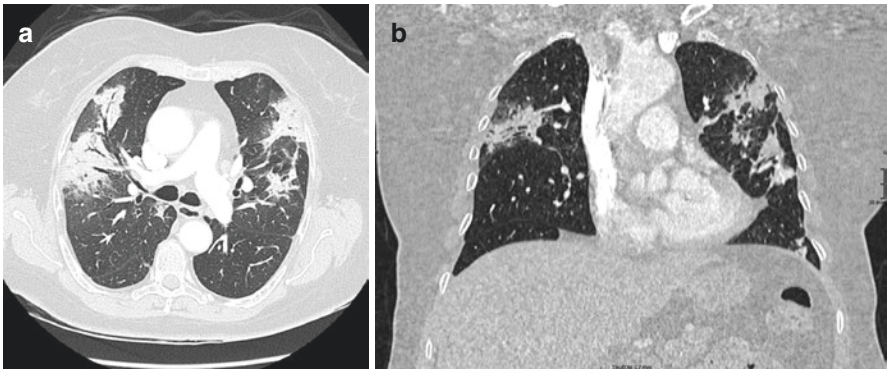

Fig. 9.23 (**a**) Chronic eosinophilic pneumonia: bilateral multiple irregular regions of consolidation (GGO) in the periphery of the lungs with air bronchogram. (**b**) Chronic eosinophilic pneumonia (coronal reconstruction): bilateral multiple irregular regions of consolidation air bronchogram

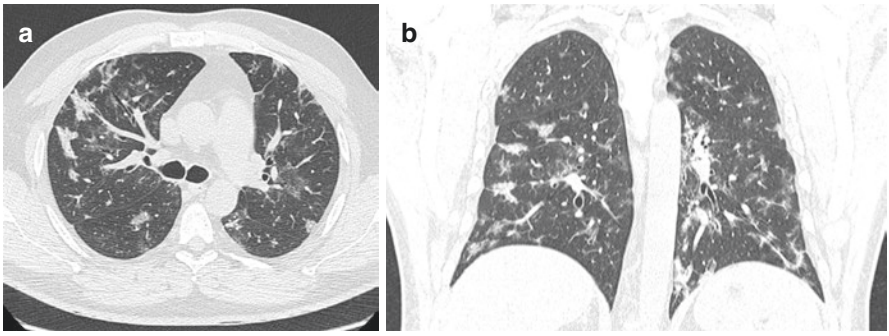

Fig. 9.24 (**a**) Organising pneumonia: bilateral multiple regions of consolidations and GGO peribronchovascularly. (**b**) Organising pneumonia (coronal reconstruction): bilateral multiple patchy areas of consolidations

3. Adenocarinoma with lepidic growth: HRCT—often multifocal, whereby centrilobular opacities may merge into larger areas of GGO or consolidations. The possibility of an adenocarcinoma is indicated by the signs of a non-retreating "inflammatory infiltration" on an X-ray that does not respond to antibiotic therapy (Fig. 9.25).
4. Lymphoma: HRCT—most often involves multiple, large, smooth nodules, masses or consolidations. Clinically, B-symptoms may be present, and laboratory changes in blood count may be expressed, including a raised sedimentation rate and elevated LDH levels (Fig. 9.26a, b).

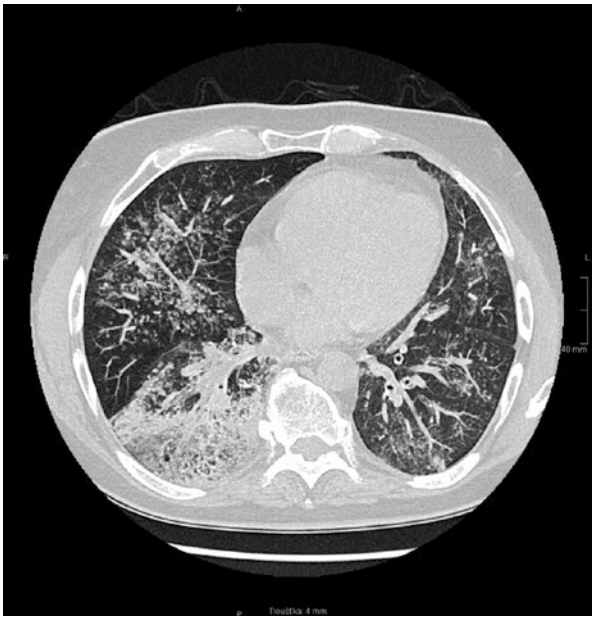

Fig. 9.25 Adenocarinoma with lepidic growth: multifocal centrilobular opacities and areas of GGO

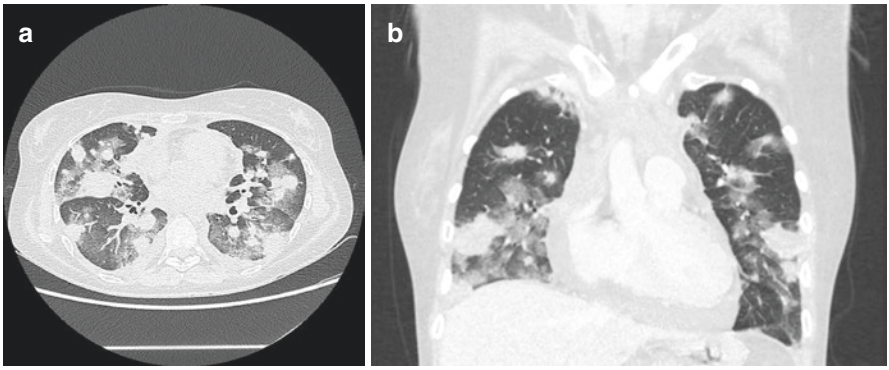

Fig. 9.26 (**a**) Lymphoma: multiple areas of consolidations and GGO. (**b**) Lymphoma (coronal reconstruction): patchy consolidations and GGO

9.5 Chronic Eosinophilic Pneumonia

Eva Kocova and Vladimir Bartos

Female, 67 years old.

The patient with recurrent bilateral pneumonia, with migratory infiltrates, that is not responding to antibiotic therapy, was sent to the clinic for further examinations and for treatment.

Medical History

- Asthma—long-term combination therapy with inhaled corticosteroids for about 5 years. In recent months, the asthma has worsened despite repeated pulse treatment with oral corticosteroids.

Occupational History and Exposure

- She previously worked as a zoo technician, and now has been working as a teacher for 6 years
- Denies any smoking, alcohol or drug abuse

History of Present Complaint

- The patient has had prolonged bilateral pneumonia, with migratory infiltrates, with symptoms of relapsing fevers and subfebrile, cough, tiredness, exhaustion, slight weight loss, exertional dyspnoea, and occasional dyspnoeic seizures. She has had repeated hospitalisations over the last 6 months and repeated antibiotic therapy which has been without beneficial effect, including anti-mycotic and anti-viral therapy, anti-tuberculous drugs and intermittent pulses of prednisone.

Objective Finding

- The patient is anxious and exhausted. On examination, there is found vesicular breathing, with mild right basal rales, otherwise no hepatosplenomegaly, no signs of bleeding, and no lymphadenopathy.

Examination

Lung Functional Test

- FVC 2.66 L/111% (ref. v), FEV_1 2.24 L/112% (ref. v), Tiff. 81%, TLC 5.09 L/108% (ref. v), RV 2.47 L/122% (ref. v), DL_{CO} 4.35/62% (ref. v), K_{CO} 1.06/70% (ref. v)
- Normal ventilation parameters. No obstructive or restrictive ventilatory disorder, and transfer coefficient for CO and transfer factor are slightly reduced

Radiology

- *HRCT of the lungs*: In the right lower lobe and the left upper lobe, there are strip-like regions of consolidation and GGO with an air bronchogram. In the mediastinum, there are increased reactive lymph nodes (Fig. 9.27a–d).

Auxiliary and Laboratory Examinations

- Haematology: sternal puncture and bone marrow trepanation performed—revealing a reactive eosinophilic syndrome without evidence of clonality or haematological malignancy.
- Infection and immunology: no parasitic involvement or other infections to explain this pulmonary syndrome. Also, there is no evidence of immunodeficiency.
- Rheumatology—without evidence of SCTD or vasculitis.
- Ophthalmology and ENT: all examinations are physiological.
- Echocardiography: normal.
- Laboratory: Intermittent mild eosinophilia in the blood count (in relation to asthma and administered per oral corticosteroid therapy), repeated elevation of CRP around 50–80 mg/L, and the total IgE is slightly increased. No further abnormalities noted.

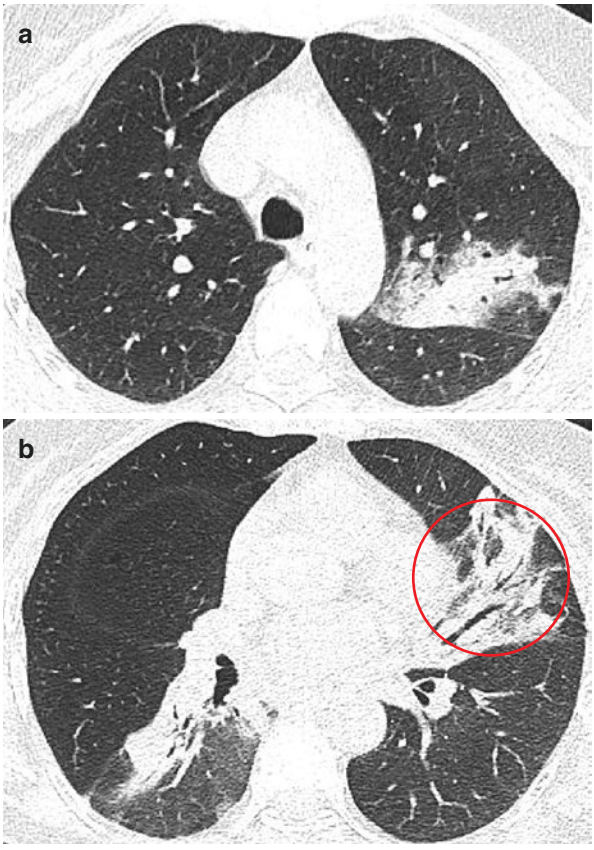

Fig. 9.27 (**a**) HRCT of the lungs: strip-like consolidations in the left upper lobe. (**b**) HRCT of the lungs: strip-like consolidations bilaterally with air bronchogram. (**c**) HRCT of the lungs: consolidations on both lungs. (**d**) HRCT of the lungs (coronal reconstruction): peribronchial consolidations with air bronchogram

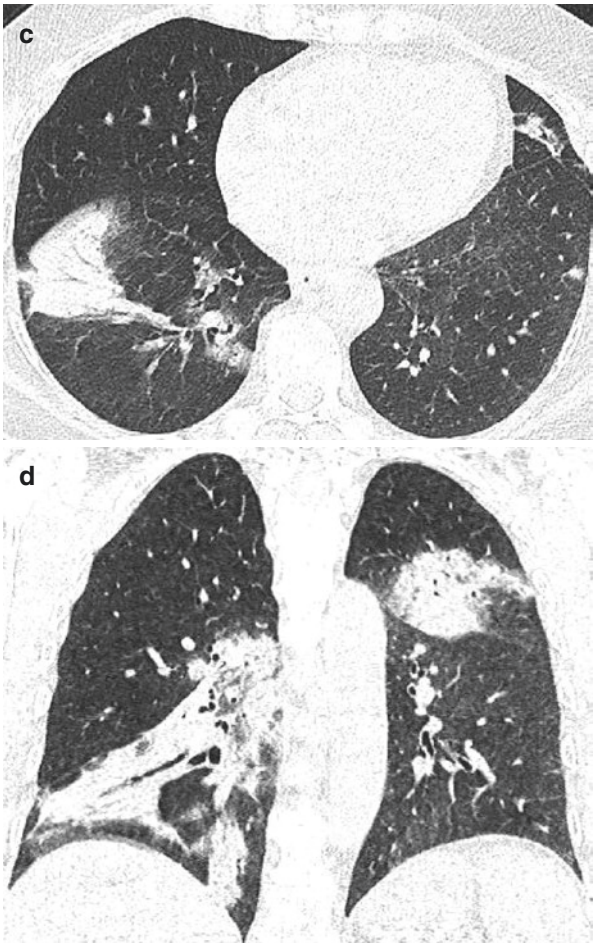

Fig. 9.27 (continued)

9.5.1 Multidisciplinary Team and Differential Diagnosis

The patient was sent from another clinic for further examinations and consultations. She has been thoroughly examined, including a bronchoscopy examination. There is repeatedly no evidence of a clear infectious agent, and she has had repeated empirical antibiotic and antimycotic therapy. For comparison, the most recent CT scan was compared with previous ones, and it indicates bilateral

migratory parenchymal consolidations. These consolidations usually have close contact with the pleura. Clinically, the patient has had prolonged fever, cough, and fatigue, despite antibiotic therapy. Laboratory findings indicate peripheral eosinophilia.

The conclusion of the MDT: Clinically and radiologically, it is probably eosinophilic pneumonitis, with organising pneumonia in the differential diagnosis. Furthermore, within the differentials, pulmonary infection or lymphoma cannot be excluded. It is recommended to perform a BAL with an examination of opportunistic infections and at the same time the execution of lung cryobiopsy.

Bronchoscopy and Bronchoalveolar Lavage

- 74% alveolar macrophages, 15% lymphocytes, 1% neutrophils, 10% eosinophils, and no malignant cells. Infectious aetiology of lung involvement was not identified in the BAL nor with PCR, and was negative for mould, opportunistic infections, or other specific infections.

Lung Cryobiopsy

- The histological image is compatible with chronic eosinophilic pneumonia, and already present are signs of fibrosis in the pulmonary parenchyma.

9.5.2 Conclusion

According to the HRCT image, the findings of the BAL and cryobiopsy were indicating chronic eosinophilic pneumonia (findings in BAL were modified by intermittent per oral corticosteroid therapy). There is no evidence of infectious aetiology, SCTD or haematological malignancy. Parenteral corticosteroid therapy at higher doses (1 mg/kg/day of prednisolone at baseline) is indicated, with a gradual reduction in the dose, after which there was rapid regression of the clinical symptoms and chest X-ray findings.

Note
Chronic eosinophilic pneumonia is an eosinophilic lung disease typically with an HRCT image of non-segmental pulmonary parenchyma consolidations, especially peripherally in the upper and middle pulmonary fields.

9.5.3 Chronic Eosinophilic Pneumonia—What We Should Consider in Differential Diagnosis

1. Organising pneumonia: Shred-like consolidations in the periphery of the lungs, typically not reaching the pleura, and rather the lower lobes are affected (Fig. 9.28).

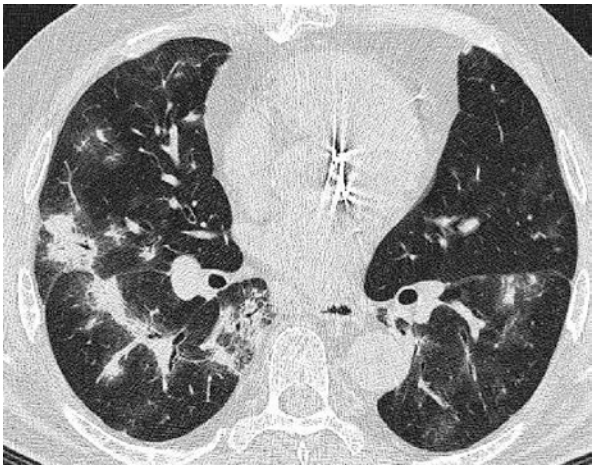

Fig. 9.28 Organising pneumonia: band-like consolidations

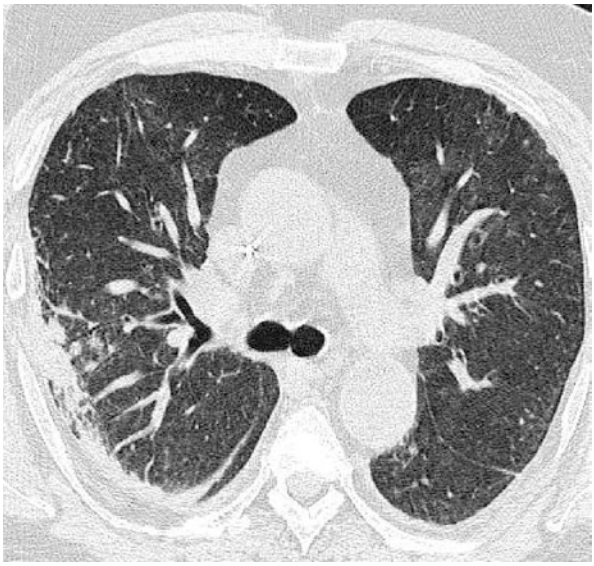

Fig. 9.29 Vasculitis: GGO and consolidations subpleurally

2. Vasculitis: GGO and pulmonary parenchymal consolidations are in a random distribution—differential diagnostics based only on the HRCT image is difficult (Fig. 9.29).
3. Bronchopneumonia: Consolidations with air bronchogram, GGO, possible coincidence with fluidothorax, and clinical signs of an acute infection (Fig. 9.30).

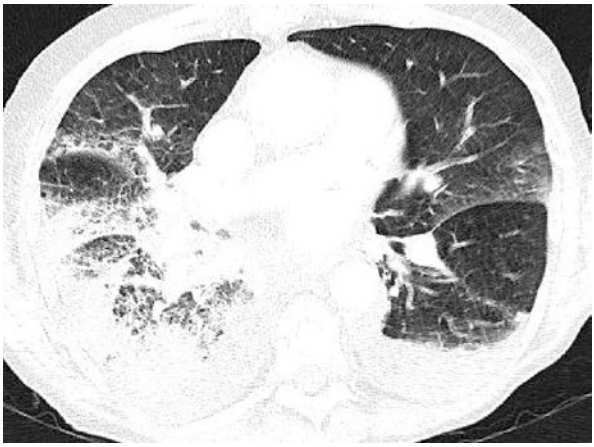

Fig. 9.30 Broncho-pneumonia: consolidations and GGO bilaterally, fluidothorax on both sides of the chest

9.6 Granulomatosis with Polyangiitis

Filip Ctvrtlik, Monika Zurkova, and Vladimira Lostakova

Male, 68 years old.

Hospitalised at the internal medicine department for suspected ANCA-associated vasculitis.

Medical History

- Until 55, he was completely healthy
- Chronic ischemic heart disease (IHD), angina pectoris (AP), NYHA I, previous subacute Q-wave inferior MI, arterial hypertension, chronic atrial fibrillation on anticoagulant therapy, good ventricular function, hypothyroidism on substitution therapy, gouty arthritis on allopurinol, hypercholesterolemia on statin therapy, and polyarthrosis.

Occupational History and Exposure

- A pensioner who worked formerly as a clerk
- Smoking history: ex-smoker

History of Present Complaint

- This 68-year-old patient was transferred from the Department of Internal Medicine, for a highly suspected cANCA-positive vasculitis. Clinically he presented with preceding arthralgia of the small joints of the hands, followed by fever within a few weeks or months. The granulomatous process in the lungs was diagnosed previously in Department of Respiratory Medicine, whereby according to a CT, multiple nodules were identified in both lobes. A bronchoscopy was performed, revealing a macroscopically fragile hyperaemic mucosa, and cytol-

ogy corresponded to the possible diagnosis of granulomatosis with polyangiitis. TB, mycobacterial and other infectious aetiology was excluded. He also reported of worsening of hypacusis.

Objective Finding

- Vesicular breathing

Examination

Lung Functional Tests
- VC 4.07 L/101% (ref. v), FEV_1 2.80 L/94% (ref. v), TI% VC_{max} 69% (ref. v), MEF25 54% (ref. v), TLC 99% (ref. v)
- DL_{CO} 62% (ref. v), DL_{CO}/V_A 72% (ref. v)
- Mild obstructive ventilatory disorder. The RV, TLC and respiratory tract resistances are in the normal range
- A slight decrease in transfer factor and transfer coefficient

Radiology
- *Posteroanterior and lateral chest X-ray*: The pulmonary parenchyma is without shadows of infiltrative changes. Lung markings are adequate. The diaphragm is smooth, with clear costophrenic angles. The heart shadow is of normal structure and size, with no mediastinal expansion.
- *HRCT of the lungs*: In both lobes, there are noticeable some small nodules. Larger nodules are presenting with cavitation (Fig. 9.31a–h).

9.6.1 Multidisciplinary Team and Differential Diagnosis

During the hospitalisation, a biopsy of the nasal mucosa was performed where ulcerations were identified, with no blood vessels in the preparation, and therefore the finding was ambiguous. Due to suspected renal impairment with creatinine levels up to 220 μmol/L, glomerular filtration of 0.43 mL/s, and mild proteinuria, a kidney biopsy was performed. Here was identified focal necrotising glomerulonephritis, with the presence of sickles and minimal sclerosis. With laboratory studies, cANCA antibodies were revealed.

9.6.2 Conclusion

The findings were closed as cANCA positive polyangiitis with granulomatosis, according to a new classification (formerly Wegener's granulomatosis), with the involvement of the kidneys, lungs, especially the upper respiratory tract, and auditory apparatus. In April 2013, pulse therapy with cyclophosphamide was initiated—in total he had twelve pulses. The disease, however, was resistant to therapy, leading to progression of the pulmonary disorder. Therefore, from May 2014 he was started on rituximab (RTX). An MRI scan of the brain, it presented with meningeal

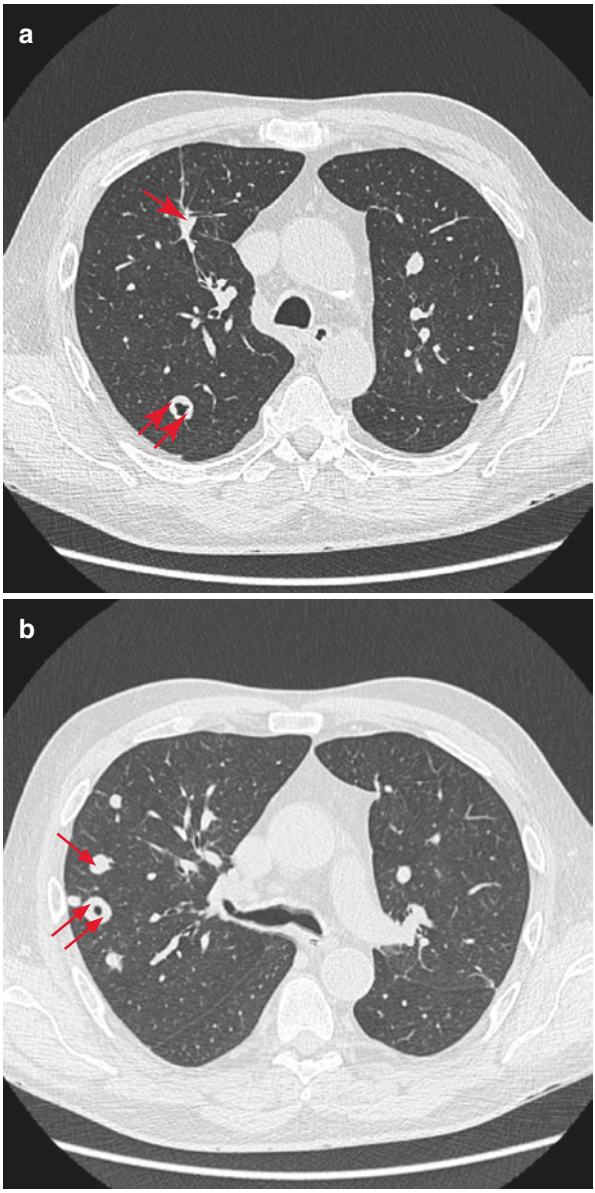

Fig. 9.31 (**a**, **b**) HRCT of the lungs: nodules in both lungs, larger one with cavitation. (**c**) HRCT of the lungs: nodules in both lungs, one with cavitation. (**d**, **e**) HRCT of the lungs: nodules in both lungs. (**f**, **g**) HRCT of the lungs (coronal reconstruction): nodules in both lungs, one with cavitation. (**h**) HRCT of the lungs (sagittal reconstruction): nodules, some with cavitation, GGO around nodules

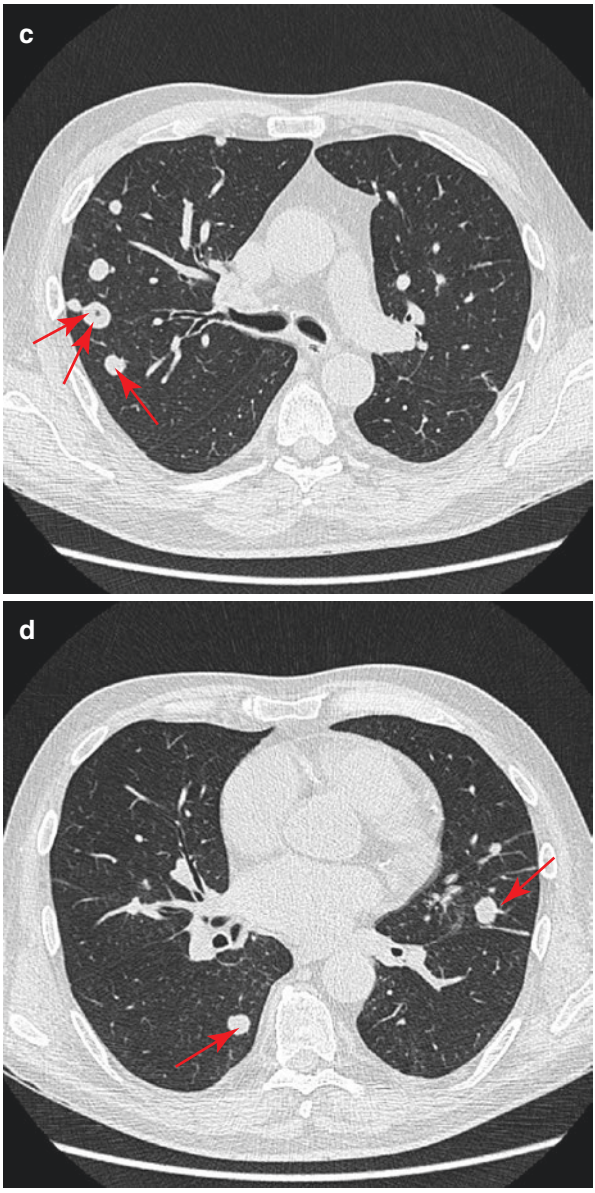

Fig. 9.31 (continued)

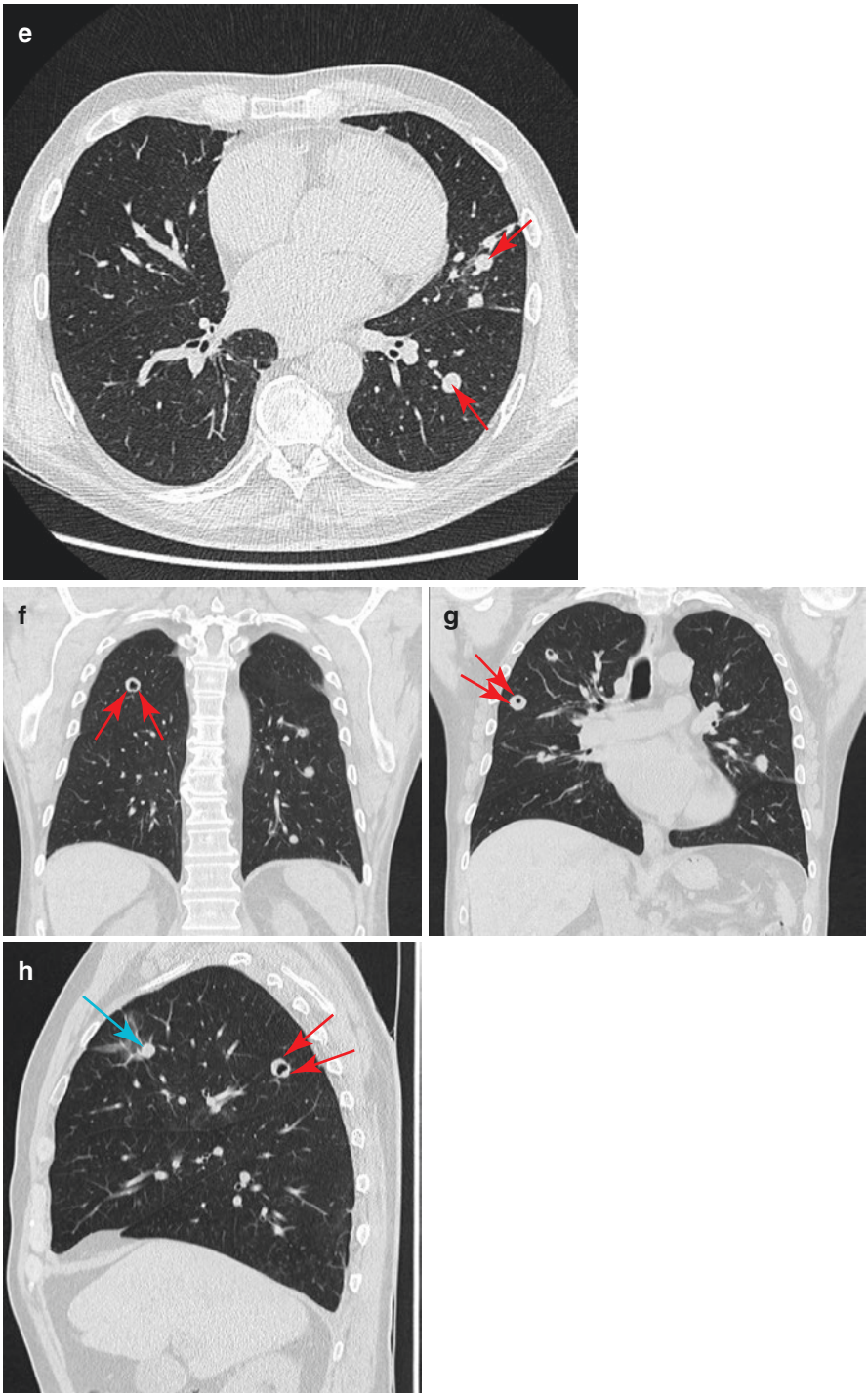

Fig. 9.31 (continued)

granulomatous involvement, and pulses of methylprednisolone were administered, and RTX was continued, with an interval on the 24th of June. The patient was also provided with azathioprine.

Note

- HRCT findings of bilateral multiple cavitated nodules with simultaneous recurrent inflammation involving the ENT and renal insufficiency, indicate granulomatosis with polyangiitis.
- As there is the presence of multiple cavitated lesions with current clinical manifestations of inflammation, it is necessary to consider TB, abscesses, septic emboli, or mycotic infections.

9.6.3 Granulomatosis with Polyangiitis—What We Should Consider in Differential Diagnosis

1. Tuberculosis: Cavities and consolidations predominate in the upper lobes or apical segments of the lower lobes. Simultaneously, the tree-in-bud nature is often seen during the endobronchial spread of the infection (Fig. 9.32a, b).
2. Metastases: Mostly multiple bilateral nodules. Clinically known primary origin. Mucinous adenocarcinoma with lepidic growth (Fig. 9.33a, b).
3. Pulmonary Abscess: Spherical nodule often with a hydroaeric level, unlike tumours, and it has a thinner, more regular inner contour. Clinical and laboratory signs of inflammation are present (Fig. 9.34).
4. Septic emboli: Multiple bilateral cavitated nodules. Due to the haematogenous spread, a feeding vessel sign may be present. The cause may be infectious endocarditis (Fig. 9.35).

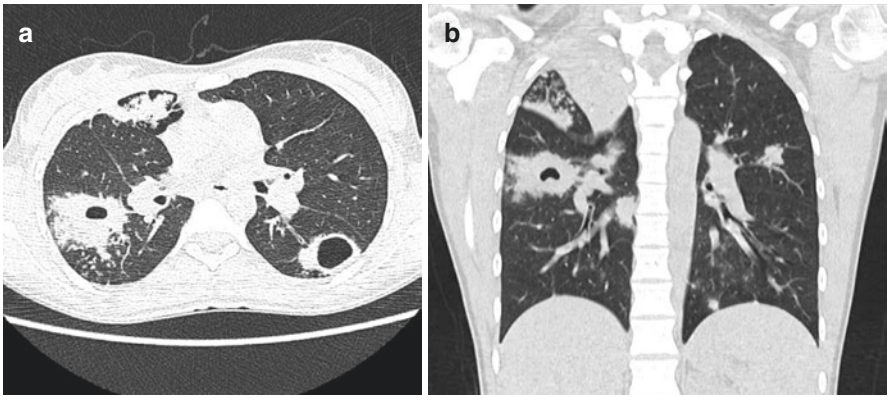

Fig. 9.32 (**a**) TB: consolidations with cavitation in the upper lobes and apical segments of the lower lobes. (**b**) TB (coronal reconstruction): consolidations, some of them with cavity

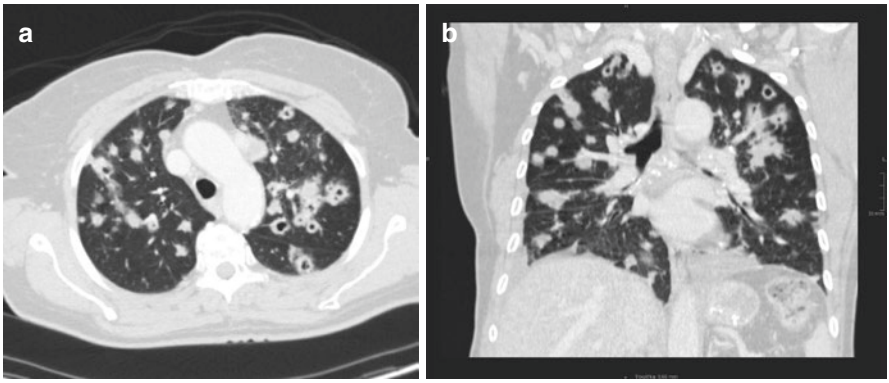

Fig. 9.33 (**a**) Metastasis: multiple nodules with cavities. (**b**) Metastasis (coronal reconstruction) multiple nodules with cavities

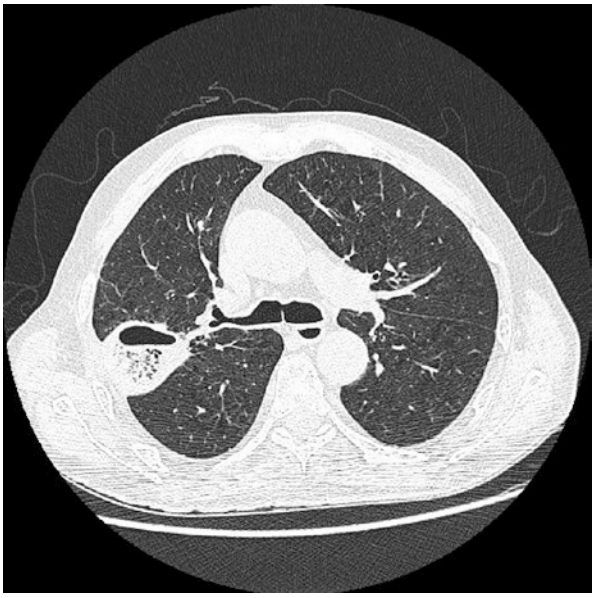

Fig. 9.34 Abscess: nodule with cavity and with a hydroaeric level in the right lung

5. Lung carcinoma: The cavity has usually an irregular inner contour and a thicker wall of irregular width. It is often solitary and larger in size. On the periphery of the tumour there are usually radial extensions, and there may be also apparent strip connections to the pleura or the hilum. In addition, signs of tumour dissemination may be present: enlarged lymph nodes in the mediastinum, bone metastases or in the adrenal glands and liver (Fig. 9.36).
6. Bronchiectasis: On axial scans, bronchiectasis can imitate cystic lung diseases; therefore it is advised to review the CT scan in multiple planes, as in bronchiectasis there is an apparent continuity with the bronchial tree (Fig. 9.37).

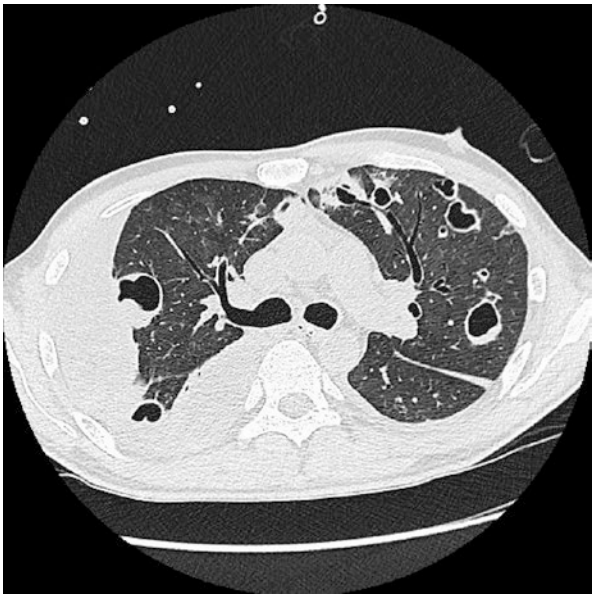

Fig. 9.35 Septic emboli: Multiple bilateral cavitated nodules, fluidothorax on the right

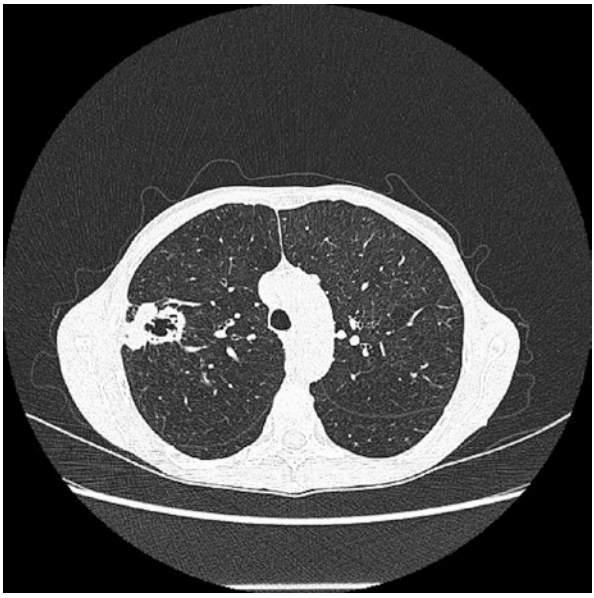

Fig. 9.36 Lung carcinoma: consolidation with cavity

7. Laryngotracheal papillomatosis: Bilateral multiple cystic formations of bizarre shapes with a wall of irregular width. They mostly occur dorsally and basally. They may merge into larger cysts (Fig. 9.38).
8. Traumatic pneumatocele: This occurs in severe chest trauma. Often, other serious traumatic changes are present at the same time: lung contusion, pneumothorax, hemothorax, and rib fractures (Fig. 9.39).

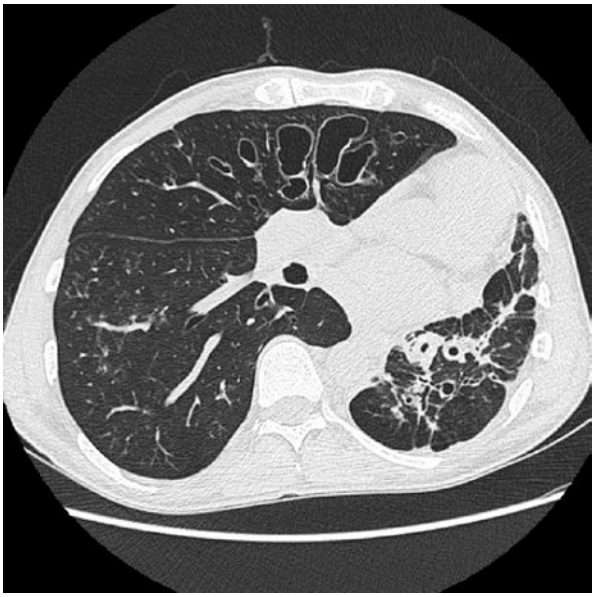

Fig. 9.37 Bronchiectasis: bilateral bronchiectasis, in the left lower lobe with thickening of the bronchial wall

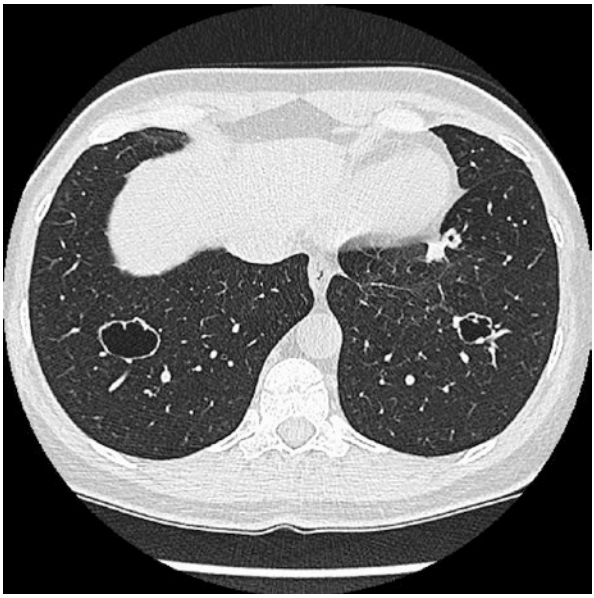

Fig. 9.38 Laryngotracheal papillomatosis: Bilateral multiple cystic formations of bizarre shapes with a thick wall

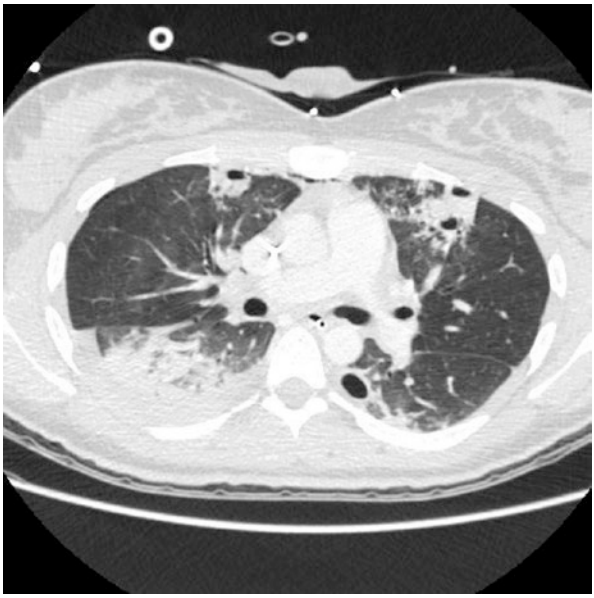

Fig. 9.39 Traumatic pneumatocele: consolidations, GGO—contusions, some with cavity—pneumatocele

9.7 Desquamative Interstitial Pneumonia

Eva Kocova and Vladimir Bartos

Male, 50 years old.

Patient admitted for examination for a finding of coarsened pulmonary markings on the posteroanterior chest X-ray.

Medical History

- Hypertension, type 2 diabetes mellitus—diet controlled

Occupational History and Exposure

- Welder (monitored by the occupational disease department for vibration injury)
- Smoking history: 15–20 cigarettes a day for 20 years, denies smoking for the last 4 years
- Pharmacological history—usual antihypertensive drugs without any pneumotoxic risk

History of Present Complaint

- For the last 2 years, he has had a progressive productive cough, expectorating white phlegm, with occasional vomiting. Also, during the last 2 years, he sometimes has night sweats, fevers (especially after intense welding) and worsening exertional dyspnoea.

Objective Finding

- No resting dyspnoea. He has vesicular breathing and basal rales that are greater on the right side. All other findings are normal.

Examination

Lung Functional Tests
- VC 3.31 L/76% (ref. v), FEV_1 2.80 L/76% (ref. v), Tiff. 80%, TLC 5.83 L/93% (ref. v), RV 2.34 L/129% (ref. v), DL_{CO} 6.83/68% (ref. v)
- Slight reduction of vital capacity, no restrictive or obstructive ventilatory disease is expressed, and the transfer factor for CO is slightly reduced

Radiology
- *HRCT of the lungs*: Bilaterally, relatively symmetrical GGO, more in the lower lobes, where also centrilobular smoothly bounded sub-solid nodules are located (Fig. 9.40a–d).

Auxiliary and Laboratory Examinations
- Rheumatological screening is negative.
- Allergological and immunological examinations: type III hypogammaglobulinaemia of unclear aetiology, absolute lymphopenia is not present, a slight decrease of CD4+ T lymphocytes, HIV negative, no other abnormalities identified.
- Haematological examination without evidence of a pathological finding.

Bronchoscopy, Bronchoalveolar Lavage and TBB
- 72% alveolar macrophages (30% positive iron stain, with positive smoker's pigment), 8% lymphocytes, 18% neutrophils, 2% eosinophils, and malignant structures are not found
- The TBLB captures only minimal inflammatory changes of the pulmonary parenchyma, and is microbiologically negative, including PCR for atypical bacterial, viral and fungal agents (including pneumocystis)

9.7.1 Multidisciplinary Team and Differential Diagnosis

The patient presented with a chronic cough and extensive GGO on HRCT of the lungs, with evidence of mild and clinically insignificant immunological abnormality, without evidence of SCTD. The BAL was without evidence of an infectious agent. The findings do not correspond to EAA.

The conclusion of the MDT: According to the clinical-radiological view, the finding is unclear. It is possible to consider however desquamative pneumonia in a former smoker working at risk in welding. It is recommended to perform VATS with a lung biopsy to definitively determine a diagnosis.

VATS and Histology

- Histological signs of desquamative interstitial pneumonia.

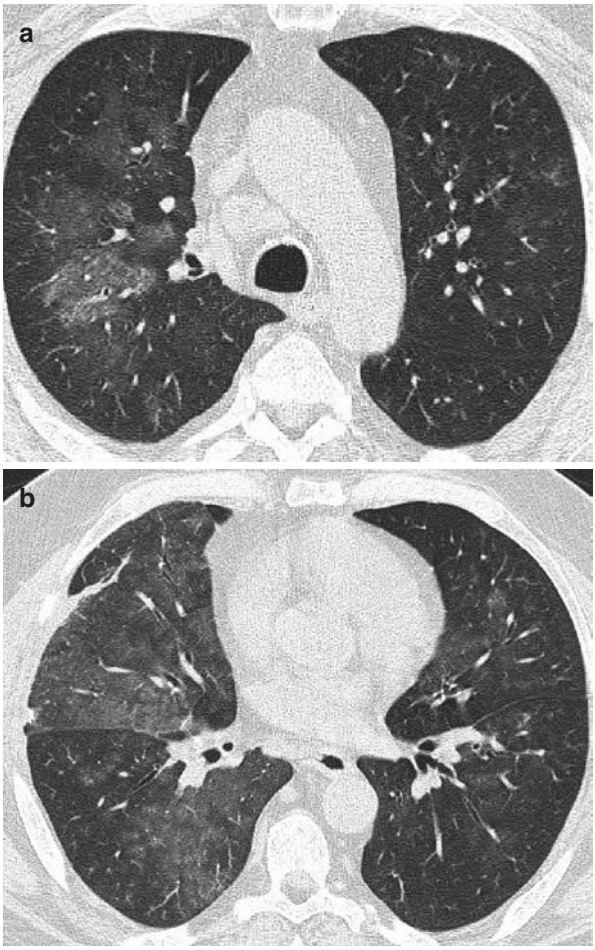

Fig. 9.40 (**a**) HRCT of the lungs: patchy areas of GGO bilaterally. (**b**) HRCT of the lungs: GGO areas bilaterally. (**c**) HRCT of the lungs: patchy GGO areas. (**d**) HRCT of the lungs: GGO bilaterally

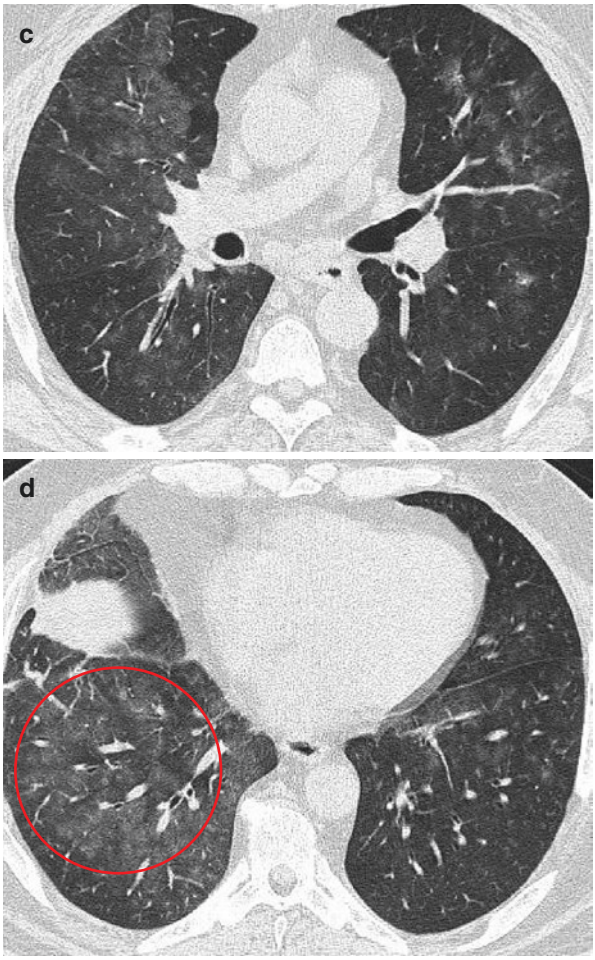

Fig. 9.40 (continued)

9.7.2 Conclusion

According to the HRCT and lung biopsy results, the findings were concluded as a desquamative interstitial pneumonia. The patient has been given a treatment regime—firstly to avoid smoke-filled areas, and to terminate his job in welding. Immunologists administered substitution therapy with intravenous immunoglobulins (for the development of recurrent infections, especially extrapulmonary involvement in the subsequent period after the diagnosis of DIP). Subsequently, there was a subjective gradual retreat of the symptoms, and HRCT of lungs confirmed the partial regression of GGO (Fig. 9.41).

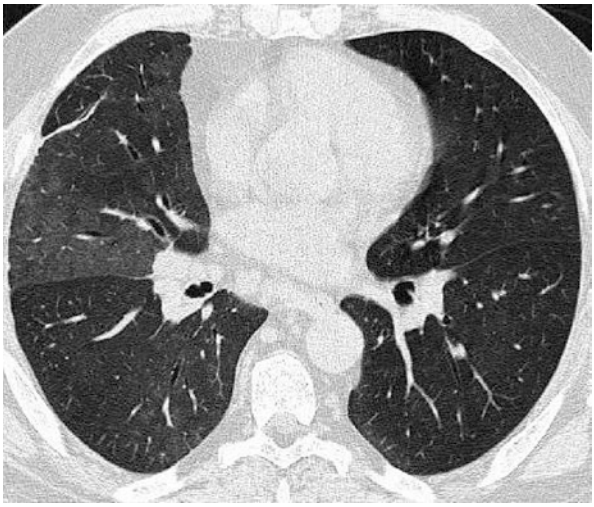

Fig. 9.41 Follow-up HRCT after 2 years—regression of ground glass opacities

Note

- Desquamative interstitial pneumonia belongs to the differential diagnostics of GGO on HRCT of lungs. It occurs especially in smokers with predisposition—rheumatoid arthritis, immunodeficiency, occupational exposure.
- On HRCT of the lungs, symmetrical regions of GGO are present, especially peripherally and basally.
- It may be associated with the occurrence of pulmonary emphysema.

9.7.3 Desquamative Interstitial Pneumonia—What We Should Consider in Differential Diagnosis

1. Opportunistic infections (e.g. CMV infection): In immunosuppressed individuals, on HRCT dispersed GGO, consolidations, and reticulations may be present (Fig. 9.42).
2. Alveolar haemorrhage: In the acute stage, regions of GGO further to the signs of crazy paving pattern (Fig. 9.43).
3. Acute interstitial pneumonia: Bilateral symmetrical regions of GGO, with a clinical image of respiratory infection, fevers, subjective myalgia and arthralgia (Fig. 9.44).
4. Eosinophilic pneumonia: Bilateral regions of GGO, eventually centrilobular nodules (Fig. 9.45).

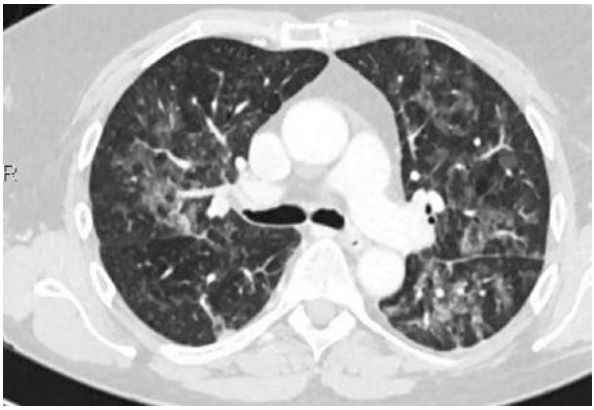

Fig. 9.42 CMV infection: areas of GGO in both lungs

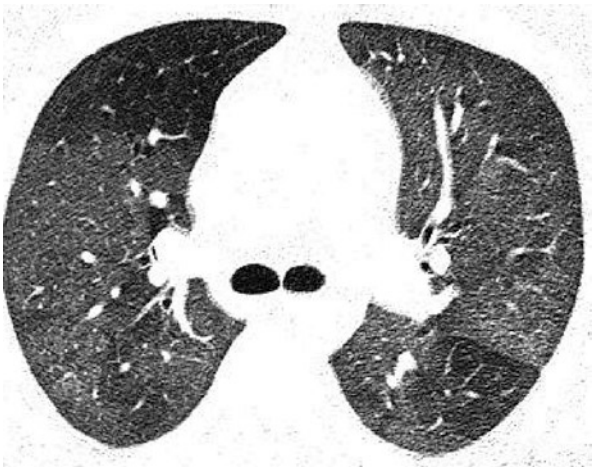

Fig. 9.43 Alveolar haemorrhage: regions of GGO

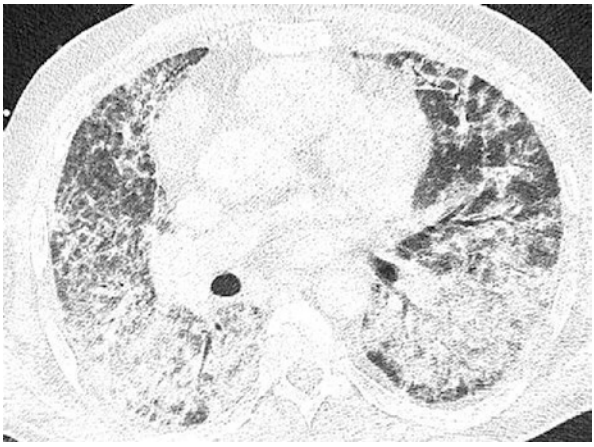

Fig. 9.44 Acute interstitial pneumonia: Bilateral symmetrical regions of GGO and consolidations

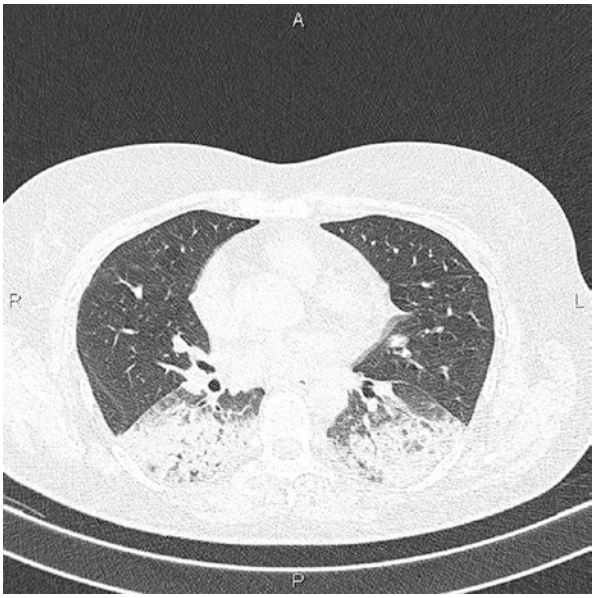

Fig. 9.45 Eosinophilic pneumonia: Bilateral areas of GGO and consolidations

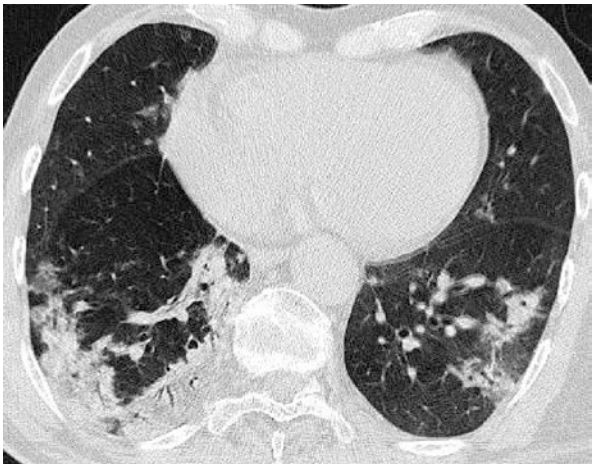

Fig. 9.46 Adenocarcinoma with lepidic growth: consolidations with air bronchogram

5. Adenocarcinoma with lepidic growth: Smoothly bounded nodules, consolidations with positive air bronchogram, GGO—histological verification required (Fig. 9.46).
6. Vasculitis: GGO and consolidations in a random distribution—differential diagnosis based only on the HRCT image is difficult to almost impossible (Fig. 9.47).

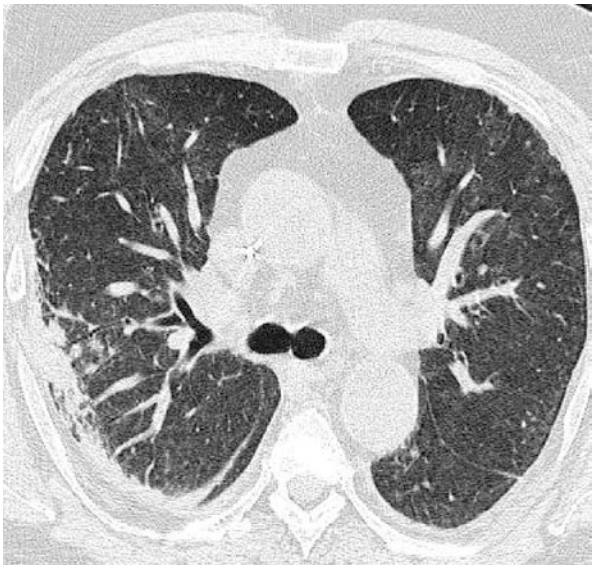

Fig. 9.47 Vasculitis: GGO and consolidations in the periphery of the lung

9.8 Acute Interstitial Pneumonia

Martina Sterclova, Jana Votrubova, and Eva Kocova

Female, 18 years old.

Has been referred for further care. The patient has been treated for EAA since the age of 17 years, and is being treated with systemic corticosteroids.

Medical History

- Observed by a neurologist for headaches
- Treated for EAA for a year, diagnosis based on HRCT findings and BAL (8% alveolar macrophages, 60% lymphocytes, 31% neutrophils, and 1% eosinophils). Autoantibodies were negative at the time of diagnosis (ANA, ENCA, ENA, and anti-dsDNA). The inducing agent was not identified, and the disease had a good clinical response to systemic corticosteroid therapy.

Occupational History and Exposure

- Unemployed—currently a student at a grammar school, lives with her mother, does not have any pets, and she does not go to swimming pools or whirlpools
- Smoking history: lifelong non-smoker
- Medication: uses prednisone 15 mg every other day, salmeterol/fluticasone 25/50, and omeprazole

History of Present Complaint

- At the age of 17, she began to breathe heavily during PE lessons, could not climb up the staircase, could not walk to the bus stop, fainted on exertion, and has a cough. Based on the examination, a diagnosis of EAA was determined, and systemic corticosteroids were initiated. She now attends a new school and states a worsening of the breathing difficulties in connection with the heating at the school. At times, she has pain in her knees.

Objective Finding

- Bilateral vesicular breathing, without secondary phenomena. On the chest, abdomen, and arms, there are vast excoriations v.s. steroid acne.

Examination

Lung Functional Tests

- FVC 1.77 L/50% (ref. v), VC_{max} 1.92 L/54% (ref. v), TLC 3.47 L/73% (ref. v), DL_{CO} 3.94/43% (ref. v).
- Moderate reduction of vital capacity, a mild restrictive ventilatory disorder, and transfer factor is moderately reduced—mainly due to the loss of alveoli.

Radiology

- *HRCT of the chest prior to systemic corticosteroid therapy initiation*: Bilateral symmetrical GGO associated with centrilobular to panlobular distribution, without signs of fibrosis (Fig. 9.48a–d).

Autoimmunity and Exposure Screening

- ANA negative, ENA negative, anti-dsDNA negative, anti-nucleosome highly positive: 183 U mL (0–19 U/mL), increased RF in the IgM class (3 times more than the standard) and IgG class (2 times more than the standard), positive ANCA PR3 (EIA), high serum specific IgG to bird feathers, and chicken serum protein (>200 mg/L).

Spiroergometry

- The load tolerance is lowered, and the circulatory response is adequate. Cardiac output dynamics, including ventricular function, are reduced. The ventilatory response is marginally increased at a higher ventilation/perfusion ratio, which is decreasing towards the normal range. A mild mechanical limitation is present. Oxygenation remains in range, and the probability of pulmonary hypertension is negligible. The overall physical condition is reduced. The findings correspond to the clinical diagnosis, with impaired respiratory mechanics, and the clinical status of the patient significantly influences the outcome of the examination.

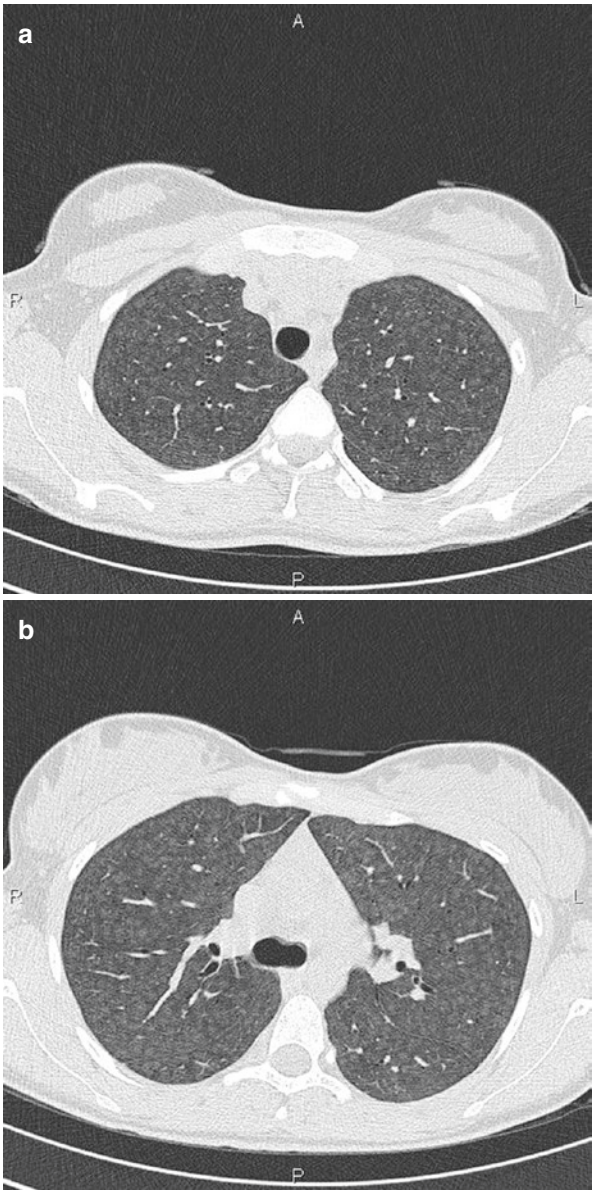

Fig. 9.48 (**a**) HRCT of the chest: centrilobular to panlobular GGO. (**b**) HRCT of the chest: bilateral symmetric centrilobular to panlobular GGO. (**c**) HRCT of the chest: centrilobular GGO, bare fissures. (**d**) HRCT of the chest: bilateral symmetric centrilobular to panlobular GGO

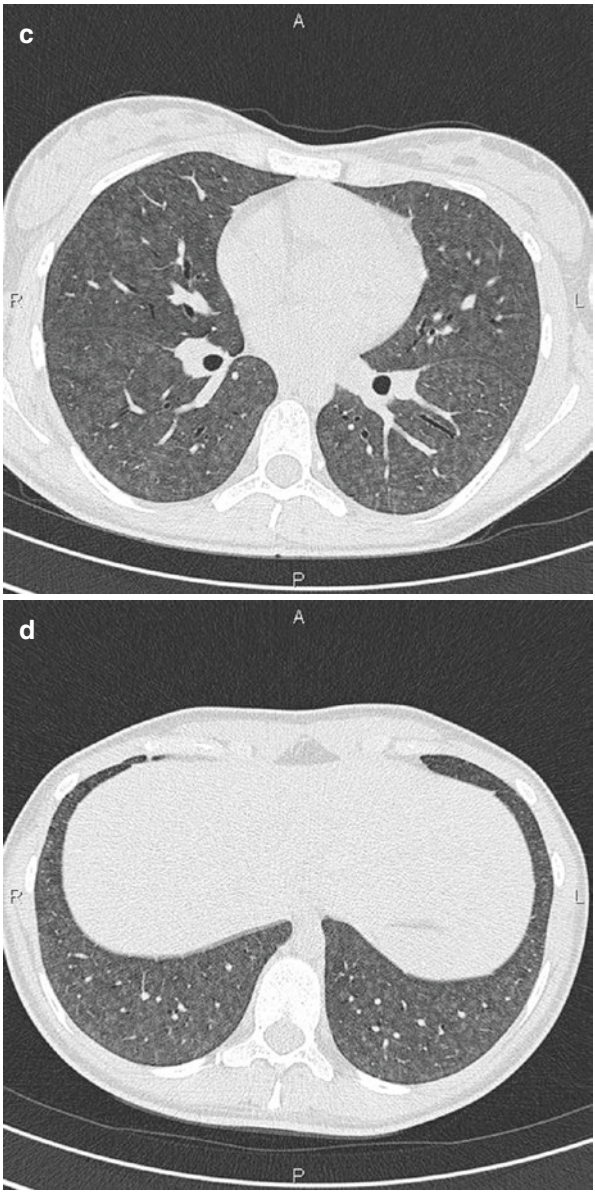

Fig. 9.48 (continued)

Consultation in Time

- From the respiratory point of view, the patient feels well, but a more pronounced skin exanthema has appeared, worsening after sun exposure.

Bronchoscopy with Bronchoalveolar Lavage

- Foamy macrophages, huge foreign body cells, alveolar macrophages 30%, lymphocytes 65%, and eosinophils 5%.

Auxiliary and Laboratory Examinations

- Rheumatological Examination: Some of the clinical criteria for systemic lupus erythematosus (SLE) are met, including fever, lung involvement, anti-histone antibodies, and ANCA. The skin findings are not typical for SLE and there is no leukopenia.
- Neurological Examination: Neurological examinations were performed due to headaches, altered states of consciousness, and for convulsions that were reported by the patient. The complete examination included an CNS MRI, MRA of the cerebral arteries, EEG, carotid ultrasound and echocardiography—all normal. The cause of the patient's symptoms was not identified by the neurologist.
- Dermatological Examination: Performed after a bus journey with direct sun exposure, the patient experienced a flare-up of symptoms on the nose and cheeks, with sharp-lined erythematous deposits and translucent vascular marking.

9.8.1 Multidisciplinary Team with Differential Diagnosis

- SLE with dermatological involvement (butterfly erythema), with pulmonary affection of acute interstitial pneumonia nature, fever, and CNS symptoms—convulsions and consciousness disorders.
- Azathioprine was initiated, alongside the original systemic corticosteroid therapy.

The conclusion of the MDT: SLE with Acute interstitial pneumonia.

Second Lung Functional Tests

- FVC 3.19 L/88% (ref. v), VC_{max} 3.20 L/91% (ref. v), TLC 4.67 L/98% (ref. v), DL_{CO} 6.97/77% (ref. v).

9.8.2 Idiopathic Acute Interstitial Pneumonia

Idiopathic AIP is rarely met in clinical practice. The disease manifests itself as respiratory failure that follows different periods of prodromal symptoms (usually several

weeks, though can be shorter), and the cause of which cannot be detected. The radiological signs are similar to that of ARDS. Histology should prove the presence of diffuse alveolar damage (DAD) and, in particular, the absence of pre-existing fibrotic changes. Some patients have histologically demonstrated acute fibrinous and organising pneumonia (AFOP). The mortality rate of the illness is 50%, some patients develop fibrotic pulmonary involvement, but some survivors may experience complete repair of the lung tissue.

Somewhat more often, we encounter acutely developing ILD based on SCTD, a drug-induced disease, infection, or contact with inhaled antigens.

Acute and Subacute Ongoing ILD

- AIP (Hamman-Rich syndrome)
- Cryptogenic organising pneumonia (COP)
- Non-specific interstitial pneumonia (NSIP)
- Acute exacerbation of IPF
- Pulmonary manifestations of systemic connective tissue disease
- Hypersensitivity pneumonitis
- Acute eosinophilic pneumonia
- Drug-induced disorder
- Diffuse alveolar haemorrhage

Note
Patients with ILD should be monitored over a long period of time, since in some cases the correct diagnosis can be determined only by the clinical character of the disease.

9.8.3 Acute Interstitial Pneumonia—What We Should Consider in Differential Diagnosis

1. ARDS: In the acute stage, differentiation based on the radiological patterns is impossible (Fig. 9.49).
2. Infections—e.g. H1N1: Differentiation based only on the radiological signs is impossible (Fig. 9.50).

In differential diagnosis, we should also consider other diseases causing diffuse alveolar damage—for example, signs of acute interstitial pneumonia caused by drug-induced damage—their differentiation solely on radiological imaging is not possible.

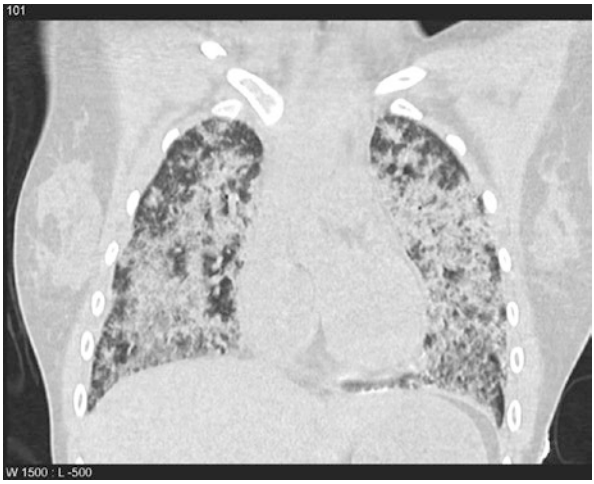

Fig. 9.49 ARDS: bilateral consolidations, GGO

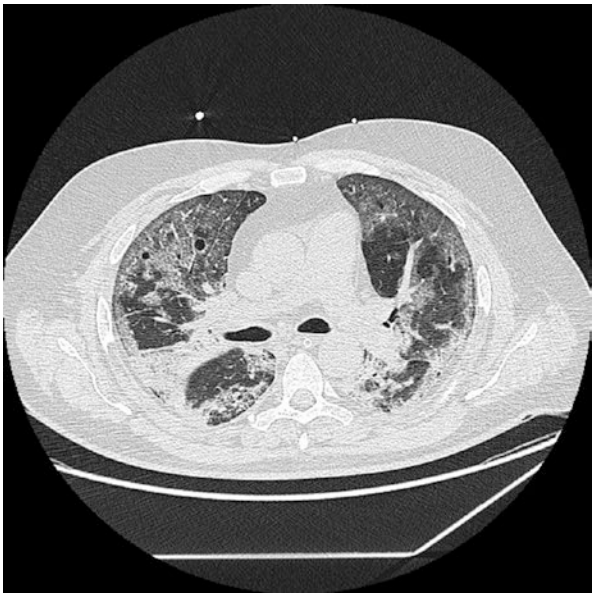

Fig. 9.50 Infection: bilateral consolidations and GGO opacities

9.9 Diffuse Alveolar Haemorrhage

Martina Sterclova, Jana Votrubova, and Eva Kocova

Male, 33 years old.

The patient presents with an unclear finding on a CT scan of the chest, without a clinical correlate.

Medical History

- Five months ago, he was hospitalised in a small hospital, for erythema nodosum and deep vein thrombosis in the left lower limb, diagnosed with antiphospholipid syndrome.
- Since the diagnosis, he has been treated with nadroparin, acetylsalicylic acid, and hepatoprotective agents.

Occupational History and Exposure

- Locksmith, welder
- Lives with his family, in a house that has a dry environment, has a dog
- Smoking history: ex-smoker for 13 years, previously smoked 20 cigarettes a day for 2 years.

History of Present Complaint

- Patient with a recent diagnosis of antiphospholipid syndrome, following recommendation of haematologist, underwent a chest CT with pathological findings. The patient denies any breathing difficulties, does not have dyspnoea, he does not cough, and has had no history of haemoptysis.

Objective Finding

- Bilaterally vesicular breathing, without secondary phenomena.

Examination

Lung Functional Tests

- FVC 5.60 L/109% (ref. v), VC_{max} 5.60 L/105% (ref. v), TLC 7.60 L/103% (ref. v), DL_{CO} 10.41/89% (ref. v).

Radiology

- *Posteroanterior chest X-ray*: Bilateral (more on the left) multiple patchy shadows, no fluidothorax, and no signs of pulmonary congestion (Fig. 9.51).
- *HRCT of the chest*: Bilateral dispersed GGO, with the costophrenic angles less affected (Fig. 9.52a–d).

Bronchoscopy, Bronchoalveolar Lavage and TBLB

- The BAL returned fluid stained with old blood, but macroscopic signs of fresh diffuse alveolar haemorrhage are not present. Cytologically, the fluid reveals alveolar macrophages 70%, polymorphonuclears 14%, and lymphocytes 8%. The identified polypoid cells are mostly cells filled with anthracotic pigment.

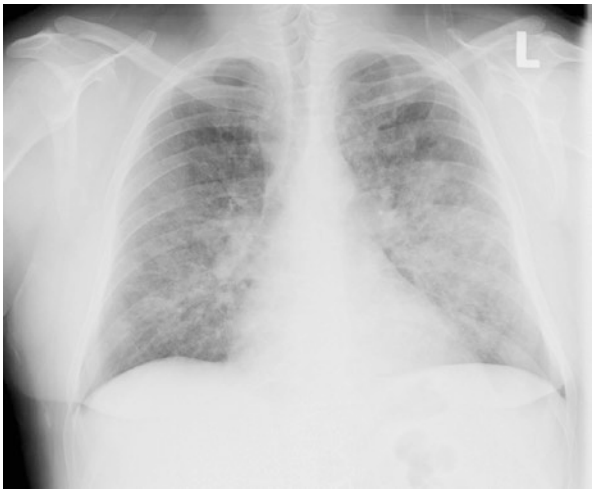

Fig. 9.51 Posteroanterior chest X-ray: patchy regions of shadows, affecting maximally perihilarly, on the left

After completing the iron staining, it is believed that this is probably haemosiderin.

- TBLB—the sample revealed a large number of siderophages in the alveoli, in the interstitium, and perivascularly. In the arteriole wall, there are haemosiderin granules accumulated within macrophages. Arteriolar wall destruction has not been found.

9.9.1 Multidisciplinary Team and Differential Diagnosis

According to the CT scan, there are bilateral GGO, with a possible corresponding image of diffuse alveolar haemorrhage. SCTD cannot be ruled out. If a renal biopsy is not indicated after completing a nephrology examination, it will be necessary to complete a surgical lung VATS biopsy.

Nephrology Consultation

- Proteinuria was captured incidentally in one sample, other samples were negative, with no erythrocyturia, and renal functions were normal. A kidney biopsy is not indicated.

VATS and Histological Examination

- This is not Goodpasture syndrome or granulomatosis with polyangiitis, the findings correspond to a veno-occlusive disease, affecting the pulmonary veins.

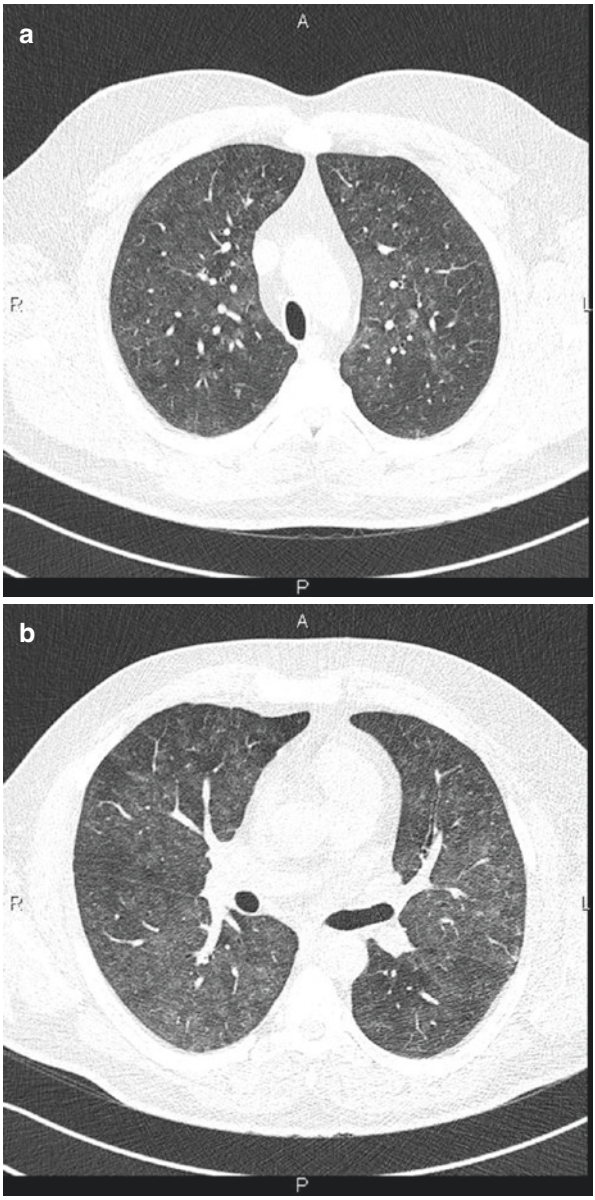

Fig. 9.52 (**a**) HRCT of the chest: bilateral areas of GGO. (**b**) HRCT of the chest: GGO in both lungs. (**c**) HRCT of the chest: bilateral areas of GGO, with less involvement in subpleural space. (**d**) HRCT of the chest: bilateral regions of GGO, with less involvement of the costophrenic angles

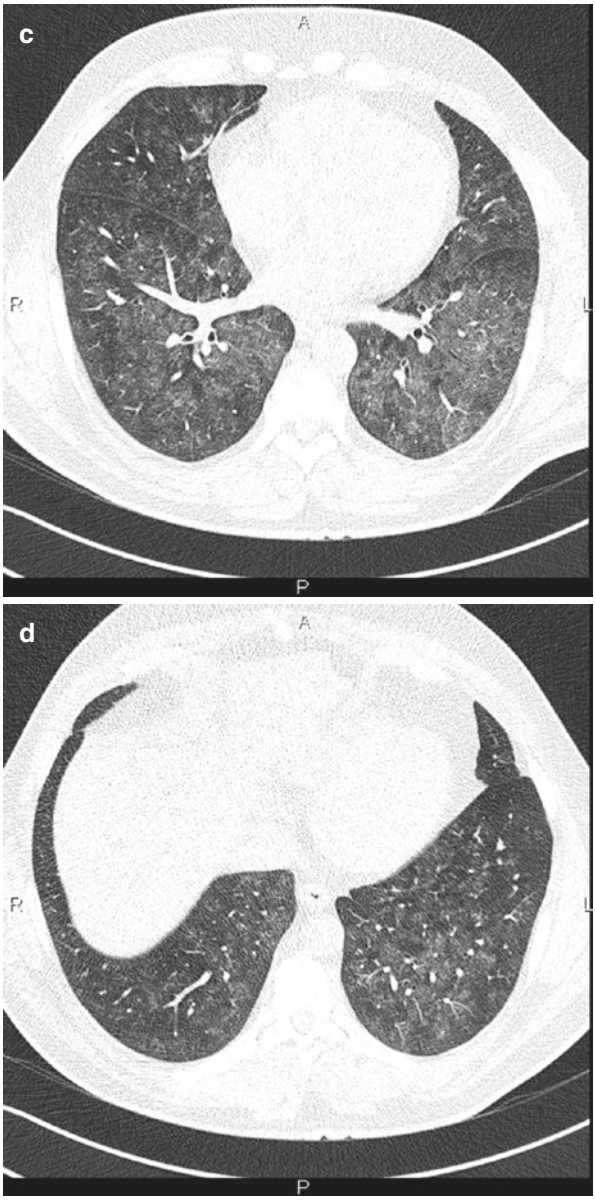

Fig. 9.52 (continued)

9.9.2 Conclusion

Considering the patient's background of deep vein thrombosis of the left lower limb and erythema nodosum, this is antiphospholipid syndrome. Long-term antiplatelet and anticoagulation therapy is recommended.

9.9.3 Diffuse Alveolar Haemorrhage

Clinical and radiological images may be quite non-specific, and furthermore, as soon as the bleeding terminates, the findings disappear relatively quickly. Regression is faster than in the case of infectious inflammation but slower than in patients with pulmonary oedema. Bronchoscopy is one of the examinations that will usually aid the exclusion/confirmation of the presence of blood in the alveoli. Differential diagnostics will also help distinguish DAH from infection and other sources of bleeding (Table 9.1). Characteristic in many cases is the macroscopic finding, with progressive haemorrhagic fluid obtained by aspiration after the instillation of individual portions of lavage fluid in BAL. It is important to note that if an acute stage of DAH disappears, this finding may be missed—if there is a strong suspicion, it may be appropriate to complete further examinations that may elucidate the presence of haemosiderin-laden macrophages. The suspicion is the capture of more than 20% of macrophages containing haemosiderin.

Table 9.1 Differential diagnostics of DAH

Immune related	Non-immune
ANCA-associated vasculitis Granulomatosis with polyangiitis Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis	Cardiac aetiology Left ventricular dysfunction Valvular defect
Capillaritis with isolated lung disorder	Infection
Side effects of treatment	ARDS
Goodpasture syndrome	Idiopathic pulmonary hemosiderosis
Systemic connective Tissue diseases Systemic lupus erythematosus Rheumatoid arthritis Inflammatory myopathies Antiphospholipid syndrome	Coagulopathy
Henoch–Schönlein purpura (IgA vasculitis)	Post-radiation damage
Cryoglobulinaemia with vasculitis	Occupational exposure
Behçet's disease	Inhalation of cocaine
Lung transplant rejection	Bone marrow transplantation
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	
Drug-induced disorder	
Bone marrow transplant	

ARDS acute respiratory distress syndrome

The pulmonary manifestation of antiphospholipid syndrome includes, in addition to DAH, pulmonary infarcts based on embolisation, pulmonary hypertension, ARDS, pulmonary artery thrombosis (including veno-occlusive disease) and capillaritis. Diagnosis of pulmonary veno-occlusive disease is based on a histological finding. It is necessary to be cautious of an eventual indication of pulmonary hypertension treatment in patients with this disease, as after initiation of the treatment, pulmonary oedema may occur.

Note

- Diffuse alveolar haemorrhage does not have to be accompanied by haemoptysis; in addition, if it subsides, the relative radiological findings also rapidly adjust and may lack the characteristic findings of progressively haemorrhagic fluid obtained by BAL. Subclinical DAH can be elucidated by iron staining of samples obtained from the BAL.
- It is important to note that bleeding into the lung alveoli is not usually a manifestation of coagulopathy, in terms of haemorrhage, but rather a case of damage to the integrity of the capillary wall of any aetiology, with subsequent thrombotic complications in the same or a different location.

9.9.4 Diffuse Alveolar Haemorrhage—What We Should Consider in Differential Diagnosis

1. Pulmonary oedema: associated with cardiomegaly and fluidothorax, smoothly thickened interlobular septa, thickened bronchial walls, and perihilar GGO are usually present (Fig. 9.53).

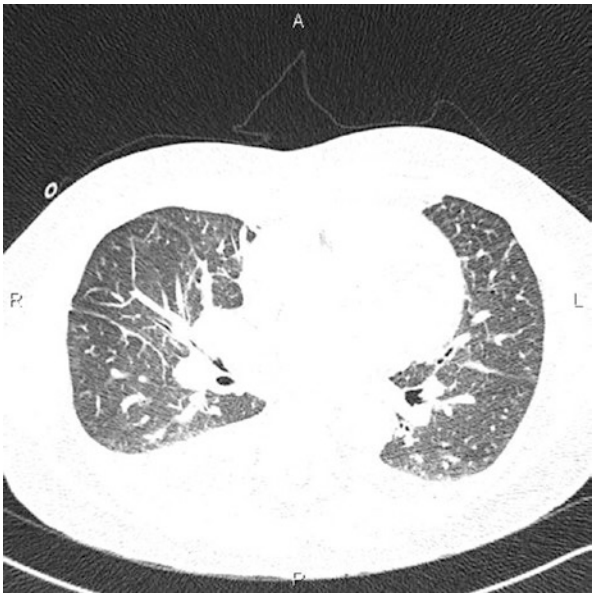

Fig. 9.53 Pulmonary oedema: cardiomegaly and fluidothorax, smoothly thickened interlobular septa, thickened bronchial walls

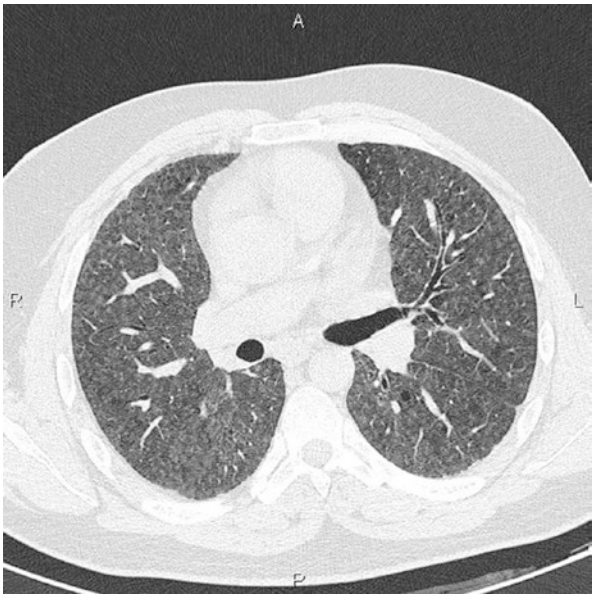

Fig. 9.54 Acute HP: bilateral centrilobular GGO

2. Acute HP: bilateral centrilobular GGO, distinction based only on the radiological image is limited (in diffuse alveolar haemorrhage, the GGO tend to be more panlobular) (Fig. 9.54).

9.10 Respiratory Bronchiolitis/Interstitial Lung Disease

Eva Kocova and Vladimir Bartos

Female, 55 years old.

The patient is presenting with a prolonged persistent cough.

Medical History

- Non-significant

Occupational History and Exposure

- Without occupational exposure, housewife (10 children), and unemployed
- Lives in the family home, keeps a cat and a budgerigar
- Smoking history: since his 15 years of age, smokes 10–20 cigarettes a day

History of Present Complaint

- Exertional dyspnoea for about half a year, with a chronic tickling cough, especially in the morning and evening, and occasionally expectorates grey phlegm.

Objective Finding

- Vesicular breathing, diffusely weakened, without pathological phenomena, no nail clubbing, and other physical findings are normal.

Examination

Lung Functional Tests

- FVC 2.10 L/82% (ref. v), FEV_1 1.56 L/73% (ref. v), Tiff. 66%, MEF50 1.62 L/45% (ref. v), TLC 4.70 L/106% (ref. v), RV 2.34 L/139% (ref. v), RV/TLC 50%, DL_{CO} 5.11/61% (ref. v), K_{CO} 1. 37/84% (ref. v)
- A mild obstructive ventilatory disorder and mild pulmonary hyperinflation. Also, a slight limitation of the transfer factor for CO. The bronchodilator test with salbutamol is negative. Exhaled NO is 6 PPB, i.e. does not indicate an eosinophilic type of inflammation in the airways.

Radiology

- *Posteroanterior chest X-ray*: Mild reduced transparency of the pulmonary parenchyma bilaterally, with slightly coarsened markings especially in the upper lung fields (Fig. 9.55).
- *HRCT of the lungs*: Bilateral heterogeneous centrilobular and paraseptal pulmonary emphysema with predilection apically. Centrilobular fine GGO, especially in the upper lobes, and the posterior costophrenic angles are entirely spared. In the upper lobes, the bronchial walls are thickened centrally. There are no signs of fibrosis. There is no significant lymphadenopathy in the mediastinum and pulmonary hila. Expiratory scans are without air trapping (Fig. 9.56a–d).

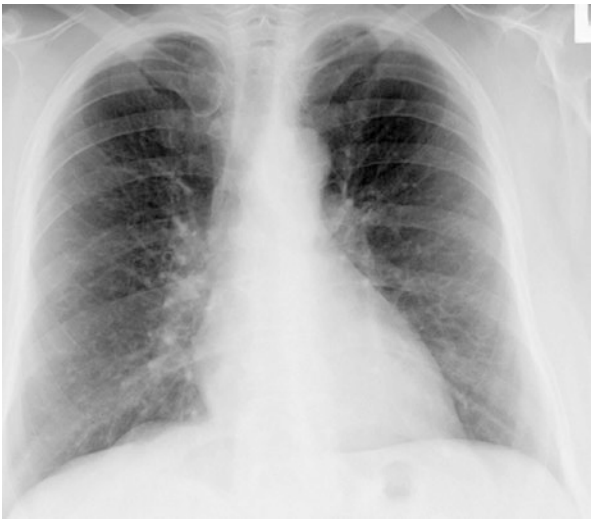

Fig. 9.55 Posteroanterior chest X-ray: slightly reduced transparency of the pulmonary parenchyma bilaterally, with slightly coarsened markings

9.10.1 Multidisciplinary Team and Differential Diagnosis

According to the HRCT, scans present heterogeneous pulmonary emphysema and centrilobular GGO, and completely omitting the posterior costophrenic angles. The patient has a history of chronic active nicotinism and is a bird keeper.

The conclusion of the MDT: Clinically and radiologically, this may present HP, and in the differential diagnosis respiratory bronchiolitis is considered. It is recommended to perform a BAL and TBLB, optimally from the upper lobes. The transbronchial biopsy was unsuccessful for technical reasons.

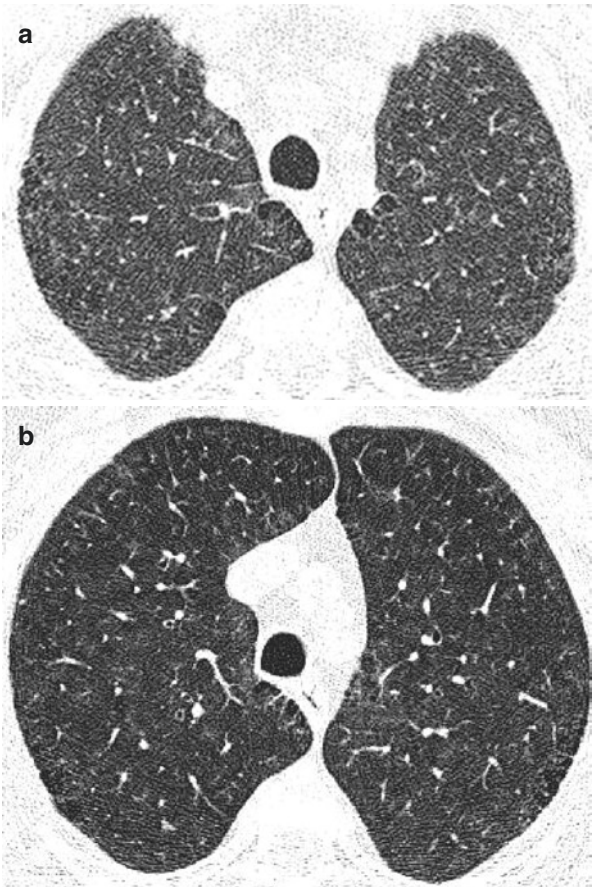

Fig. 9.56 (**a**) HRCT of the lungs: centrilobular and paraseptal pulmonary emphysema. (**b**) HRCT of the lungs: centrilobular and paraseptal pulmonary emphysema, centrilobularly fine GGO. (**c**) HRCT of the lungs: centrilobular GGO. (**d**) HRCT of the lungs: costophrenic angles without significant changes

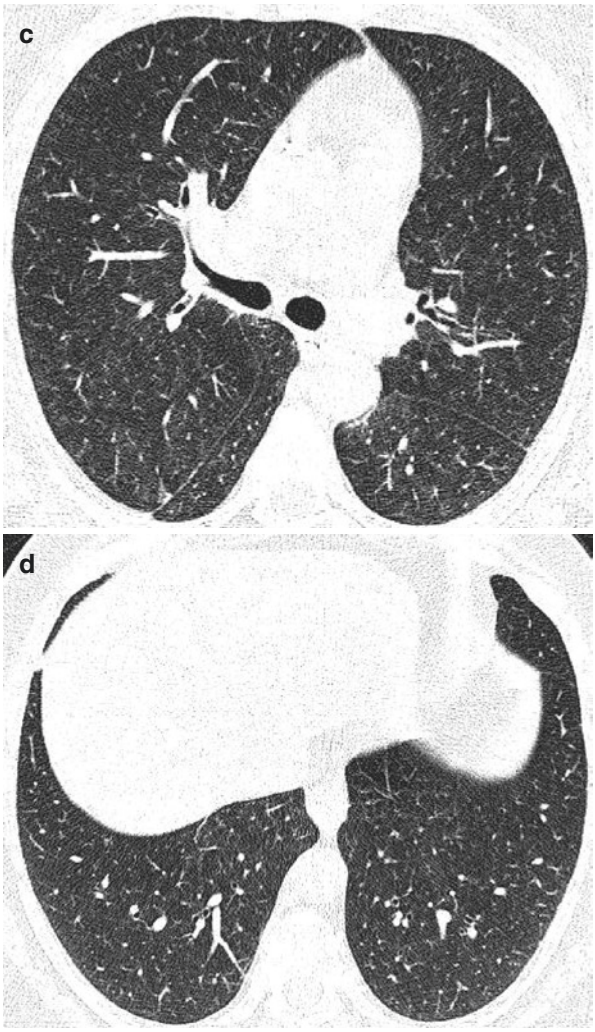

Fig. 9.56 (continued)

Bronchoscopy, Bronchoalveolar Lavage and TBLB

- 95% alveolar microphages, most of them with significant smoking inclusions, 2% lymphocytes, 3% eosinophilic leukocytes, 1% neutrophils and mast cells. Malignant tumour structures are not found. An infection has not been identified.

9.10.2 Conclusion

COPD with emphysema in an active smoker with unclear pulmonary interstitium involvement. BAL does not correspond to HP. The treatment for the COPD is recommended, with a therapeutic regime and smoking cessation. Subjectively, there is a slight improvement during the treatment; however active nicotinism persists. A follow-up HRCT of lungs was performed with stationary findings of centrilobular GGO in the field of pulmonary emphysema. Histological verification via VATS was recommended (as repeating a bronchoscopy with TBB was refused by the patient, and, a cryobiopsy was not available at that time). According to histology, signs of small airways disease of a characteristic bronchiolocentric fibrosis are present. Most probably represents smoking-related disease, RB-ILD. Findings were concluded as respiratory bronchiolitis/interstitial lung disease in a patient with COPD.

Note

- Respiratory bronchiolitis/interstitial lung disease (RB-ILD) is, according to HRCT, indistinguishable from respiratory bronchiolitis of infectious or other aetiology (toxic, inhaled), and sometimes hardly distinguishable from desquamative interstitial lung disease (as GGO coincides more).
- It belongs to smoking-related lung disease. Centrilobular densities can be expressed, however only very discreetly.

9.10.3 Respiratory Bronchiolitis/Interstitial Lung Disease—What We Should Consider in Differential Diagnosis

1. Acute HP: Differential diagnosis based on HRCT alone is difficult—centrilobular GGO and air trapping on expiratory scans are typical of HP (Fig. 9.57).
2. Lymphocytic interstitial pneumonia: poorly defined centrilobular or subpleural nodularities, thickening of interlobular septa and central peribronchovascular interstitium, thin-walled cysts typically perivascularly or subpleurally, and mediastinal lymphadenopathy (Fig. 9.58).
3. NSIP: GGO in a random distribution with predilection subpleurally and typical subpleural sparing, signs of pulmonary fibrosis—reticulations, loss of pulmonary volume, and traction bronchiectasis (Fig. 9.59).

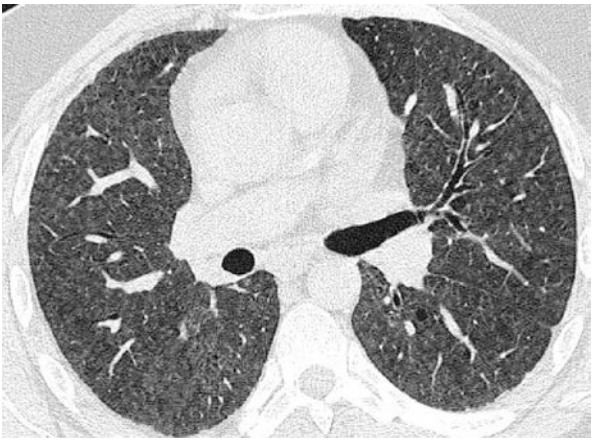

Fig. 9.57 Acute HP: centrilobular sub-solid nodules

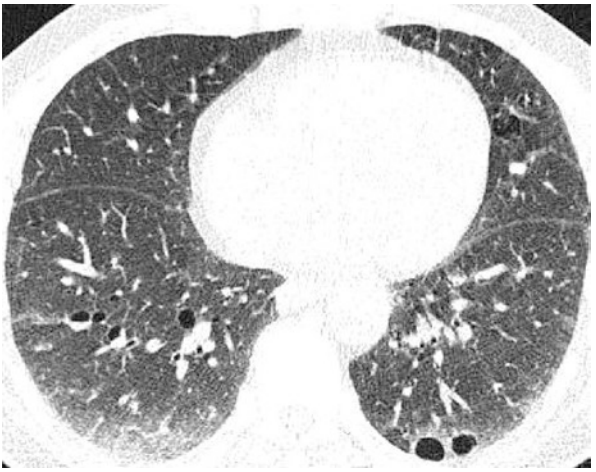

Fig. 9.58 Lymphocytic interstitial pneumonia: cysts in subpleural space and in perivascular distribution, areas of GGO

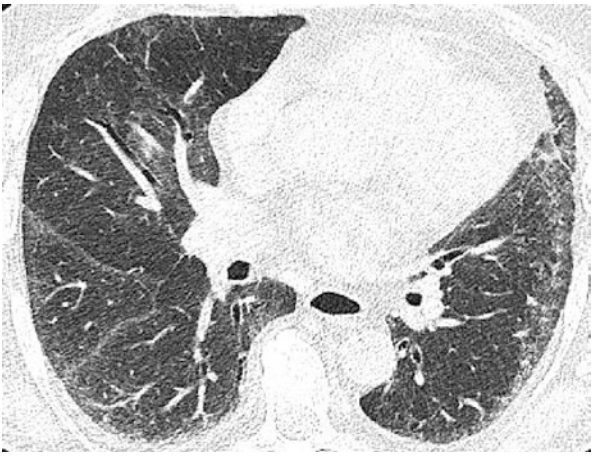

Fig. 9.59 NSIP: reticulations and GGO in subpleural space

9.11 Chronic Aspirations

Eva Kocova and Vladimir Bartos

Female, 34 years old.

The patient was transferred from a district hospital to finalise the examination of an interstitial lung disease.

Medical History

- Observed under the haematology department for several years for mild reactive polycythaemia, otherwise insignificant history.

Occupational History and Exposure

- Working without risks, in a clean environment, now on maternity leave for 4 years
- Lives in a flat with no pets, has not travelled
- Smoking history: ex-smoker

History of Present Complaint

- The patient has observed a cough for about 4 months, dry, without expectoration, no fever, and no sore throat. She does not have any swallowing difficulties; she denotes an occasional feeling of food "returning" when lying down, though denies heartburn. She is without dyspnoea, however, it is present on exertion, though states it is minimal and is not bothering her. For the cough, a chest X-ray was initially performed, where an unclear finding was obtained, therefore HRCT of the lungs was indicated. A gastroscopy was also performed, yet the case was not resolved. Now, with a 4-month delay, she observes a worsening exertional dyspnoea. The HRCT of the lungs identified progression of findings, therefore was sent to a specialist department for further investigations.

Objective Finding

- Without dyspnoea, without oxygen therapy cyanosis of the lips (disappears after the administration of oxygen). Vesicular breathing was initially completely clear; however during progression, the development of rales basally is noted. From the very beginning, the patient was identified to have clubbing in the fingers, with watch glass-shaped nails.

Auxiliary and Laboratory Examination

- Blood count values are normal (currently no polycythaemia), without eosinophilia, and the biochemical parameters are within range. There are no signs of inflammation, and no evidence of autoantibodies or immunodeficiency.

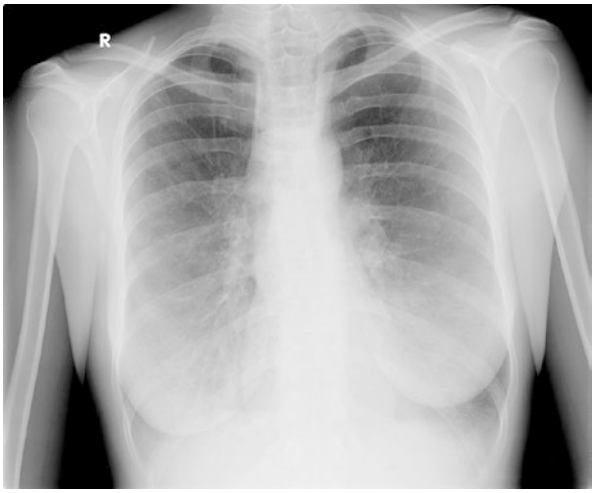

Fig. 9.60 Posteroanterior chest X-ray: basal multiple patchy shadows of the lung parenchyma

Examination

Lung Functional Tests

- Initial mild obstructive ventilatory defect, with a slight limitation of vital capacity and mild pulmonary hyperinflation
- FEV_1 1.71 L/52% (ref. v), Tiff. 67%, MEF50 1.48 L/33% (ref. v), RV 2.40 L/148% (ref. v), RV/TLC 49% (ref. v)
- No evidence of a restrictive ventilatory disorder (TLC 4.93 L/91%)
- Transfer factor (severely) and transfer coefficient for CO (moderately) impaired (DL_{CO} 3.14/33%, K_{CO} 0.88/50% (ref. v))

Radiology

- *Posteroanterior chest X-ray*: Basal multiple shadows of the lung parenchyma, more to the right (Fig. 9.60)
- *Initial HRCT of the lungs (performed 4 months ago, at the beginning of the examination process)*: Bilaterally, basally, multiple centrilobular nodules, subsolid, merging in regions of GGO (Fig. 9.61a–d). Only the apexes of the upper lobes are spared. Basally, over the diaphragm, there are regions of pulmonary parenchyma consolidations. In the mediastinum, there is a bulky dilated oesophagus, with food debris, and a hydroaeric level.

9.11.1 Multidisciplinary Team and Differential Diagnosis

The findings were consulted by the MDT, with the conclusion: according to HRCT, bilateral extensive coalescent centrilobular GGO, basal consolidations, and oesophageal dilatation—the CT signs raises the suspicion of oesophageal achalasia. The findings in the pulmonary parenchyma correspond to massive aspirations, and in a

wide differential diagnosis, the participation of infection and alveolar haemorrhage cannot be excluded. It is recommended to perform gastroscopy first to resolve the oesophageal finding, and secondly, due to the non-involuting finding, bronchoscopy with BAL and biopsy.

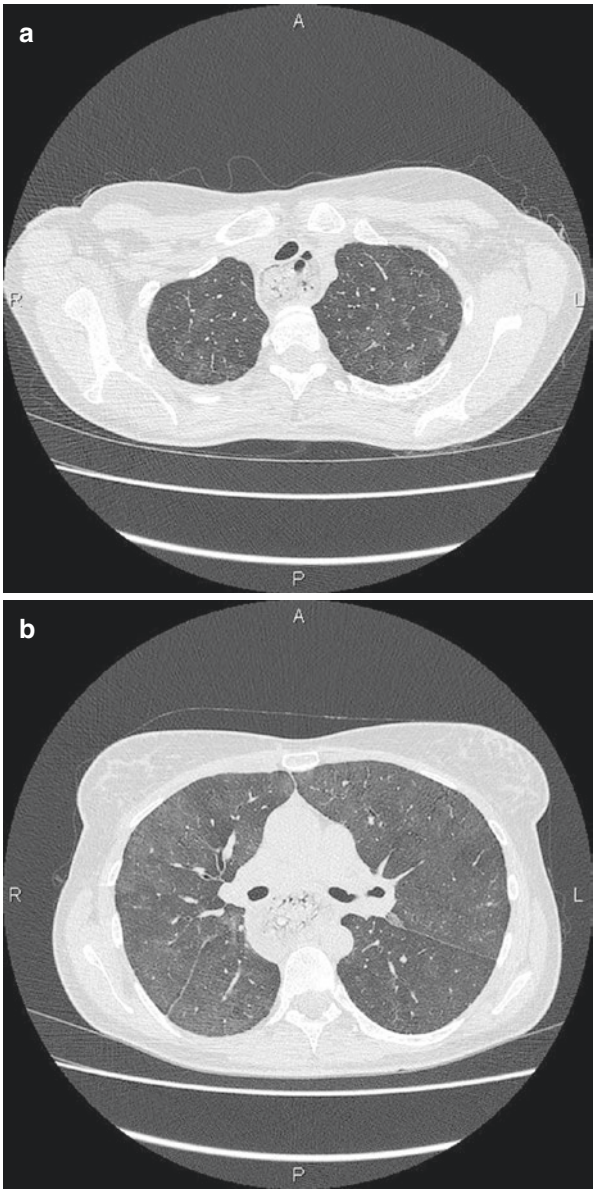

Fig. 9.61 (**a**, **b**) HRCT of the lungs: bilateral sub-solid centrilobular nodules and GGO. (**c**, **d**) HRCT of the lungs: bilateral peribronchial multiple regions of GGO to consolidations with air bronchogram

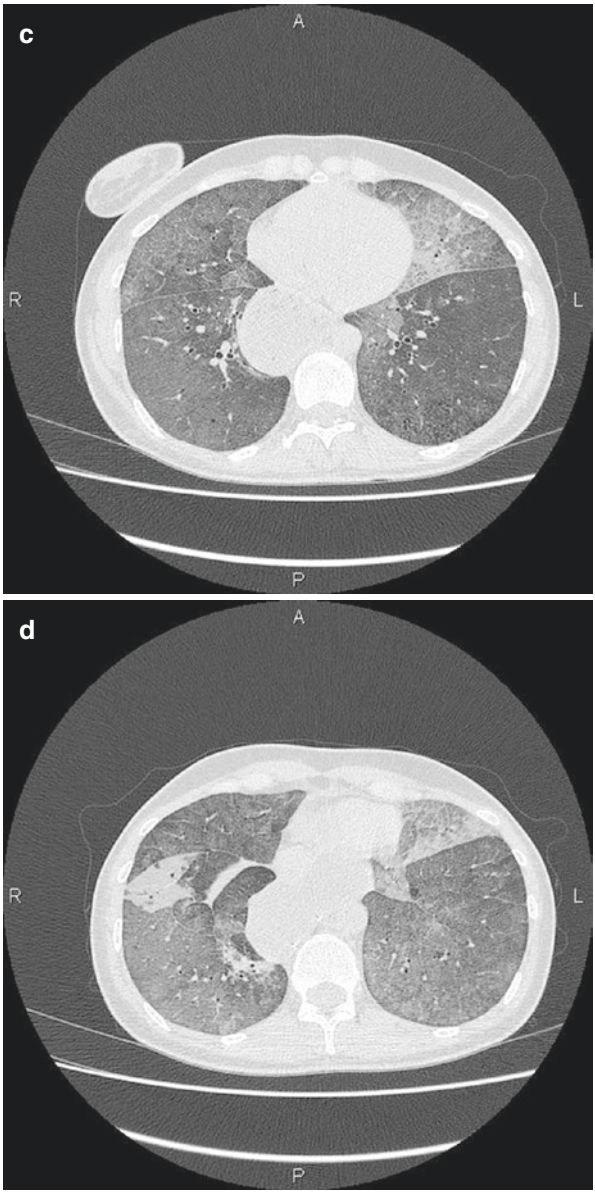

Fig. 9.61 (continued)

- *HRCT of the lungs (during symptom worsening—4 months after the first examination)*: Progression of bilateral centrilobular nodules, merging in GGO, mainly in the basal parts of the lungs (Fig. 9.62a–d). There are no reticulations. In the mediastinum prevails a pronounced dilation of the oesophagus with food debris.

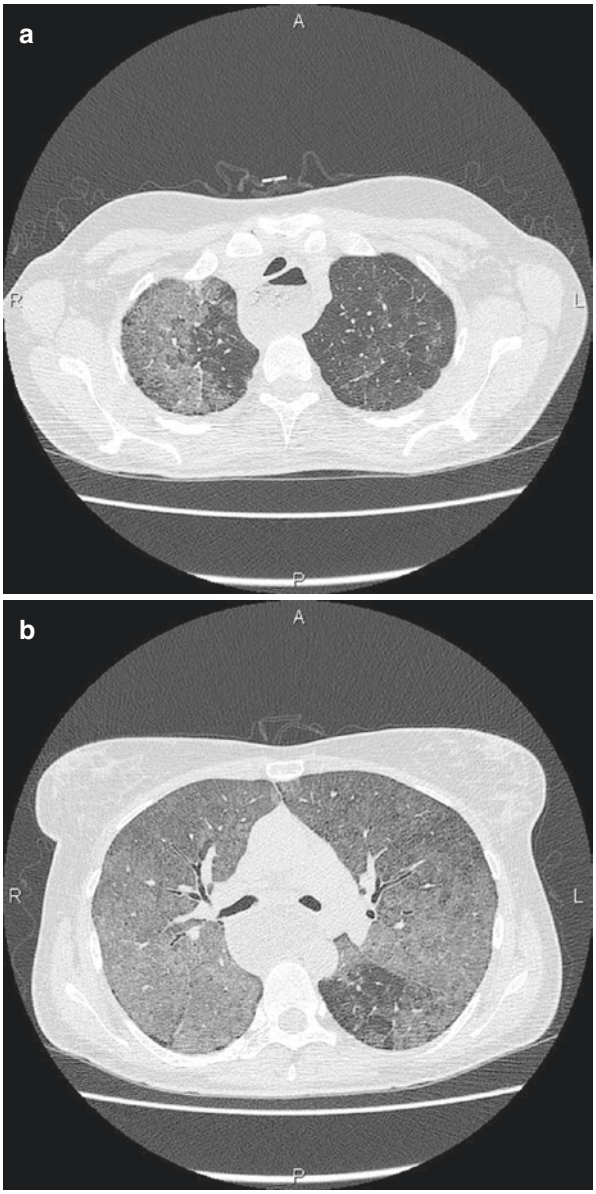

Fig. 9.62 (**a**) HRCT of the lungs (during symptom worsening—4 months after the first examination): Progression of bilateral centrilobular nodules. (**b**) HRCT of the lungs (during symptom worsening—4 months after the first examination): Progression of bilateral centrilobular nodules, merging in GGO. (**c**, **d**) HRCT of the lungs (during symptom worsening—4 months after the first examination): Progression of bilateral centrilobular nodules, merging in GGO, mainly in the basal parts of the lungs

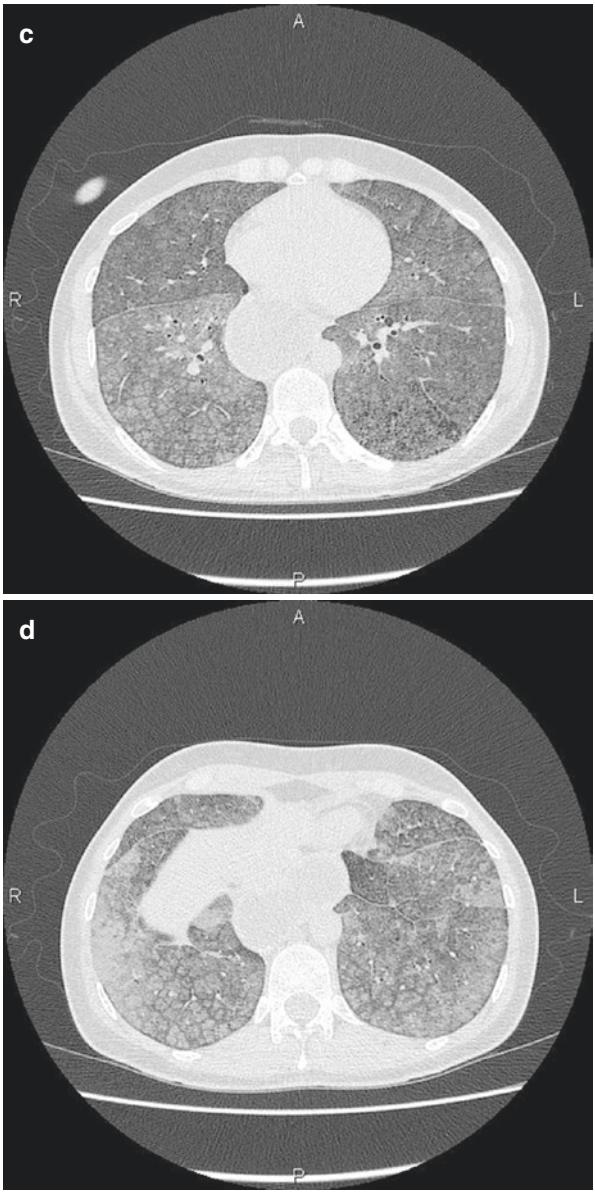

Fig. 9.62 (continued)

Bronchoscopy with Bronchoalveolar Lavage

- The initial planned bronchoscopic examination could not be performed. This was due to repeated vomiting and the risk of massive aspiration during local anaesthesia administration, regardless of appropriate preparation prior to the examination, including fasting. For this reason, a gastroscopy was initially per-

formed, demonstrating significant stagnation of food and fluids in the oesophagus. This necessitated suctioning the oesophagus content with a thick probe, and then following gastroscopic post-cleaning of the oesophagus, with the introduction of a nasojejunal tube to nourish the patient. After this preparation, a bronchoscopy was performed, revealing external tracheal depression by about 30% from the dilated oesophagus, with signs of asymptomatic aspiration of food in the trachea and central bronchi. Consequently, a BAL was performed; the lavage fluid was white-yellowish, cloudy, and sedimented in the beaker at rest, creating an upper, rich yellow layer about 5 mm deep, sharply bordered from the opaque liquid underneath. This fluid was examined by a pathologist, including using a special fat staining technique, revealing mild neutrophilic alveolitis, and large amounts of fat droplets in macrophages: an aspiration-compatible finding, and one atypical for alveolar proteinosis.

Laboratory Examination

- Signs of inflammation continue to be low, no evidence of infection. No alveolar haemorrhage has been identified.

9.11.2 Conclusion

Further examinations confirmed the radiological suspicion of repeated aspirations during oesophageal dilation in oesophageal achalasia. The lung findings progressed over time during the period of aspirations. The condition of the patient has required repeated gastroscopic interventions with the suction of congesting secretions in the dilated oesophagus. The patient requires parenteral nutrition and further enteral nourishment via a nasojejunal tube. Presently, the treatment of oesophageal achalasia is performed by pneumatic balloon dilation of the functional cardiac stenosis of oesophagus, stabilising the condition of the patient.

Note
Repeated aspirations may be clinically asymptomatic for a long time even in young patients, and on HRCT may have an image of multiple diffuse coalescent GGO.

9.11.3 Chronic Aspiration—What We Should Consider in the Differential Diagnosis

1. Pulmonary infection/pneumonia: the disease is not usually homogeneous, clinical signs vary (Fig. 9.63).
2. Pulmonary haemorrhage: radiologically cannot be reliably distinguished from aspirations (Fig. 9.64).
3. Pulmonary alveolar proteinosis: the crazy paving pattern, requires the necessary correlation of clinical, radiological and pathological images (Fig. 9.65).

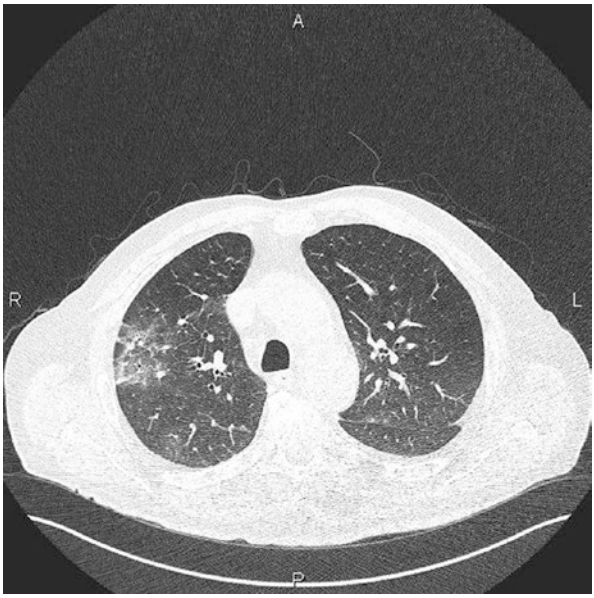

Fig. 9.63 Infection: patchy areas of GGO

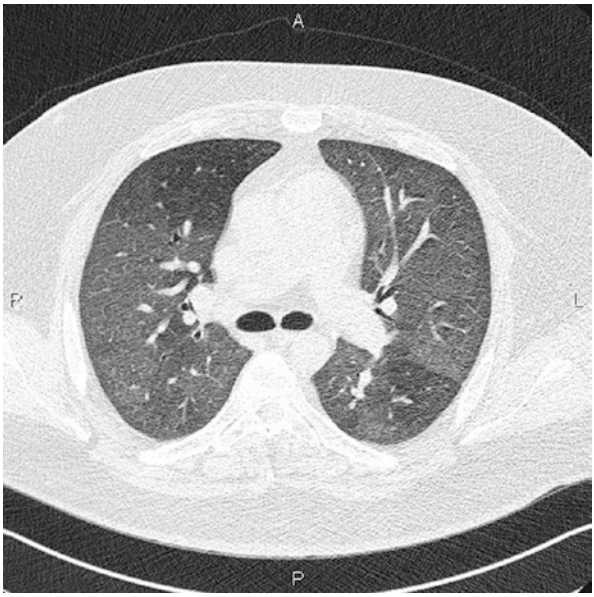

Fig. 9.64 Pulmonary haemorrhage: diffuse GGO

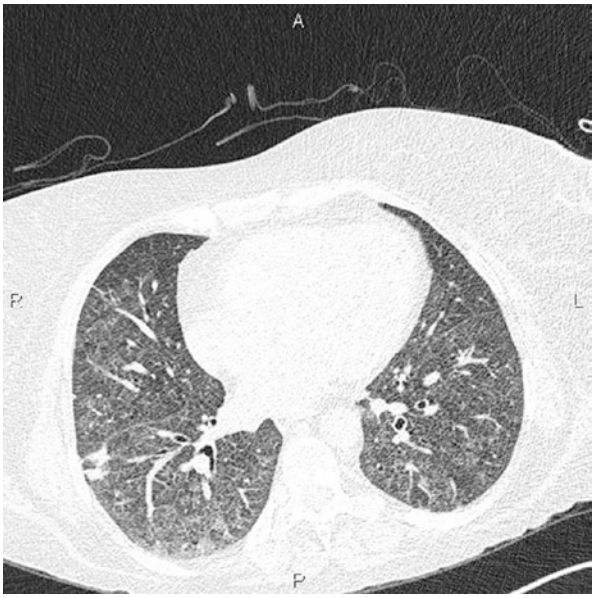

Fig. 9.65 Pulmonary alveolar proteinosis: crazy paving pattern

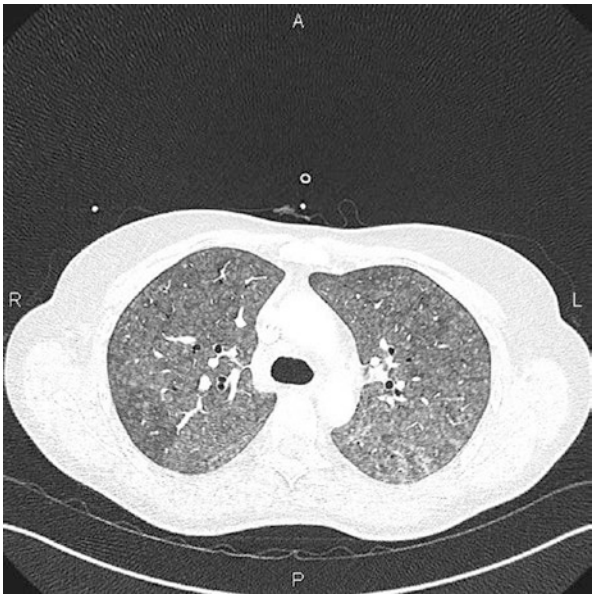

Fig. 9.66 Acute stage HP: centrilobular GGO

4. Hypersensitivity Pneumonitis: centrilobular GGO, occasionally coalescent, typically in the upper lobes with sparing of the posterior costophrenic angles (Fig. 9.66).

9.12 Pulmonary Siderosis

Eva Kocova and Vladimir Bartos

Male, 58 years old.

The patient was sent to ambulatory care at the pulmonary clinic for breathing difficulties, cough and an unclear finding on HRCT.

Medical History

- Has been treated for asthma for years—eosinophilic, atopic (difficulties persist despite treatment)
- Hyperlipoproteinaemia

Occupational History and Exposure

- Occupational exposure—lifelong welder, working in a dusty and smoky environment
- Smoking history: lifelong non-smoker, without hobbies in relation to hypersensitive pneumonitis

History of Present Complaint

- For about 10 years, the patient was treated by a local pneumologist for eosinophilic atopic asthma (ICS and LABA), and despite the treatment, exertional dyspnoea progressively worsened—leading to mild yet poor tolerance of exertion at work, at the same time a worsening dry cough, without expectoration. The patient was recurrently treated with ATB for upper respiratory tract infections, and ENT identified the presence of polyps. Subsequently, for unclear findings on HRCT of the lungs, the patient was sent to the pulmonary clinic.

Objective Finding

- Normal—vesicular breathing, patent airways, without crepitations, no nail clubbing, with no cyanosis.

Examination

Lung Functional Tests

- Mild obstructive ventilatory disorder with normal lung capacity (VC_{max} 4.45 L/86% (ref. v), FEV_1 3.00 L/77% (ref. v), Tiff. 67%, MEF50 0.76 L/37% (ref. v), with a complete regression after a bronchodilator test
- Without restrictive ventilatory disorder (TLC 7.61 L/126% (ref. v)), and a slight limitation of pulmonary diffusion for CO (DL_{CO} 8.62/78% (ref. v))
- Raised NO values in the exhaled air—Fe_{NO} 70 PPB—indicates eosinophilic inflammation in the lower respiratory tract

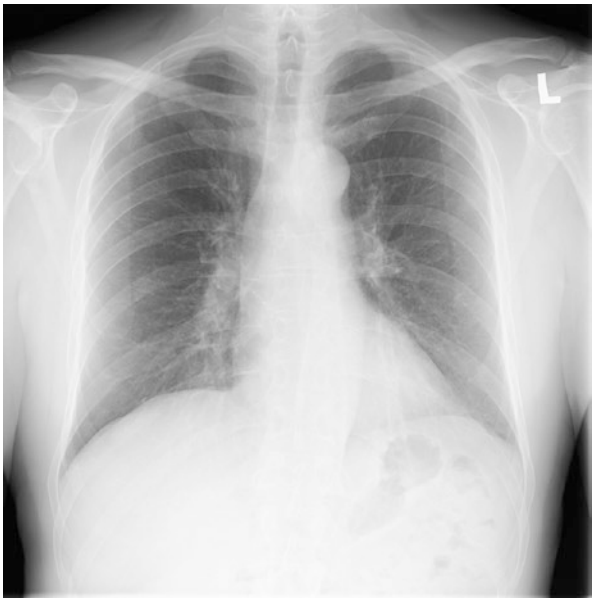

Fig. 9.67 Posteroanterior chest X-ray: very discreet, rare regions of small shadows, especially in the upper lung fields

Radiology

- *Posteroanterior chest X-ray*: Very discreet, rare regions of small shadows, especially in the upper lung fields (Fig. 9.67)
- *HRCT of the lungs*: Multiple centrilobular, very discrete nodules, sub-solid, mainly of the character of GGO. Basal, and subpleurally, rare intrapulmonary calcifications. There is no lymphadenopathy (Fig. 9.68a–d).

Bronchoscopy and Bronchoalveolar Lavage

- A normal endobronchial finding, without macroscopic evidence of diffuse alveolar haemorrhage in the BAL. Cytological staining demonstrated siderophages, with increased iron staining in 90% of macrophages. Otherwise, a normal cytological count. No infection has been identified.

Auxiliary and Laboratory Examination

- Normal blood count and biochemical parameters without evidence of inflammation. Although there is a slight elevation of total IgE (240 IU), an immunological examination did not reveal immunodeficiency.
- An allergologist confirmed atopy.
- There is no hypersensitivity to mould, etc.
- Screening for SCTD was negative.

9.12.1 Multidisciplinary Team and Differential Diagnosis

According to the findings, there are discrete centrilobular nodules diffusely in the pulmonary parenchyma, with a slight predilection into upper lobes. There are no

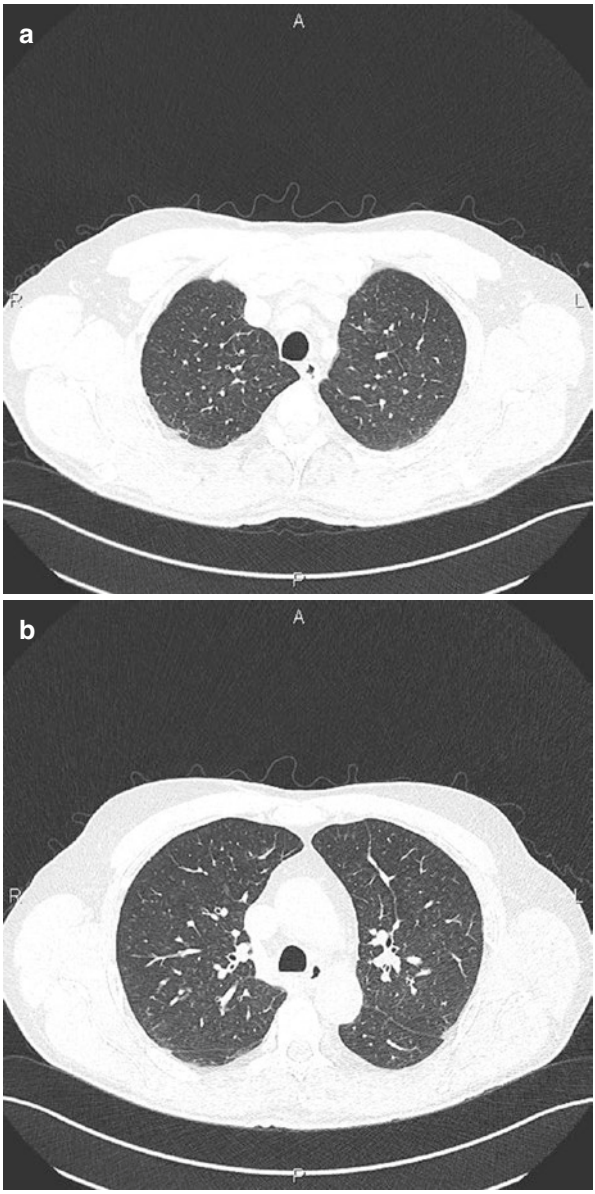

Fig. 9.68 (**a**) HRCT of the lungs: multiple centrilobular discrete sub-solid nodules. (**b**) HRCT of the lungs: multiple centrilobular discrete nodules, sub-solid. (**c**, **d**) HRCT of the lungs: rare basal intrapulmonary calcifications

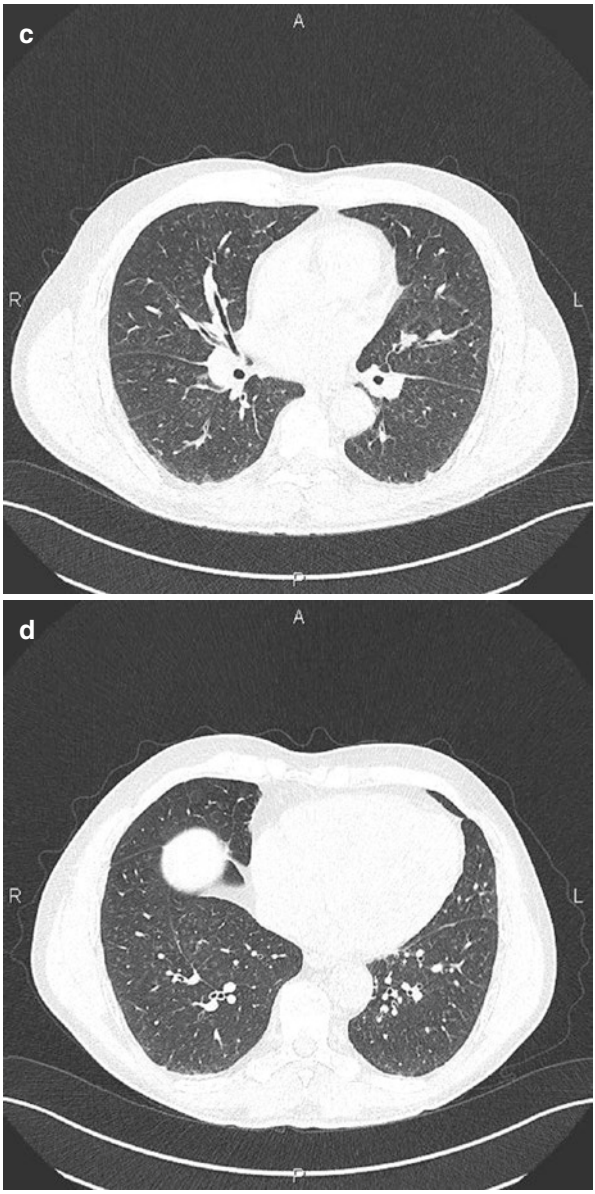

Fig. 9.68 (continued)

plaques, and no significant nodes in the mediastinum. In view of a positive occupational history and the HRCT, the findings are suspected of pneumoconiosis. In the differential diagnosis we must consider hypersensitivity pneumonitis, or bronchiolitis—although this diagnosis is unlikely.

The conclusion of the MDT: Clinically and radiologically, it is probably pneumoconiosis, and cryobiopsy is recommended.

Cryobiopsy

- Microscopic fragments of the pulmonary parenchyma are with the changes of centrilobular pulmonary emphysema, without significant fibrotic changes. Within the alveoli and interstitium, we find macrophages with coarse-grained reddish pigment, which is strongly positive on iron staining. Bronchiolitis has not been identified.
- Conclusion: iron nodules in the septa and intraalveolarly, without significant fibrotic changes—these findings are compatible with pneumoconiosis in a welder.

9.12.2 Conclusion

Due to a positive occupational history, a corresponding HRCT and compatible histopathological findings from the cryobiopsy, diagnosis of this case was determined as pulmonary siderosis in a welder (pulmonary haemorrhage or reduction in haemoglobin levels in the blood count, were not identified, and vasculitis was not confirmed, neither was a severe cardiac comorbidity).

Note

- Siderosis belongs to pneumoconiosis. Findings on HRCT of the lungs can be very discreet.
- Typically, it is not associated with lung fibrosis. With combined inhalation risk, silicosiderosis, which is already associated with pulmonary fibrosis, may develop.
- Primary pulmonary siderosis has a similar HRCT sign, but a history of exposure to weld gases is missing.

9.12.3 Pulmonary Siderosis—What We Should Consider in Differential Diagnosis

1. Complicated silicosis: associated with the occurrence of larger nodules up to masses, typically perihilarly, in the vicinity of the paracicatricial emphysema (Fig. 9.69).
2. Other pneumoconiosis: The HRCT findings are similar, and hence differential diagnosis is not possible (Fig. 9.70).

3. Miliary pulmonary tuberculosis: multiple nodules of uniform size and distribution (Fig. 9.71).
4. Hypersensitivity Pneumonitis: centrilobular nodules especially in the upper lobes with the omission of the posterior costophrenic angles, with typical patient history, and laboratory examination (Fig. 9.72).

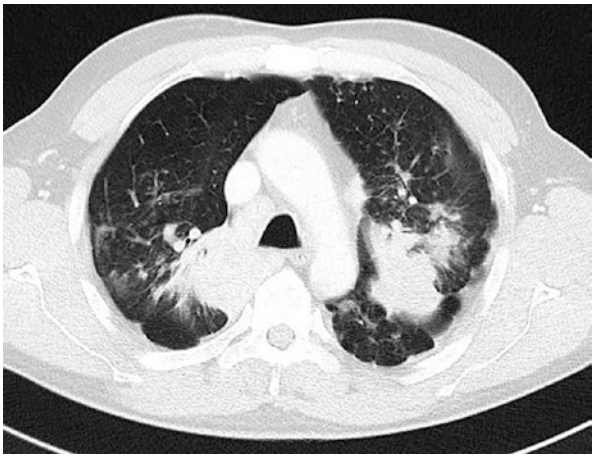

Fig. 9.69 Silicosis: bilateral masses with distorsion of lung parenchyma

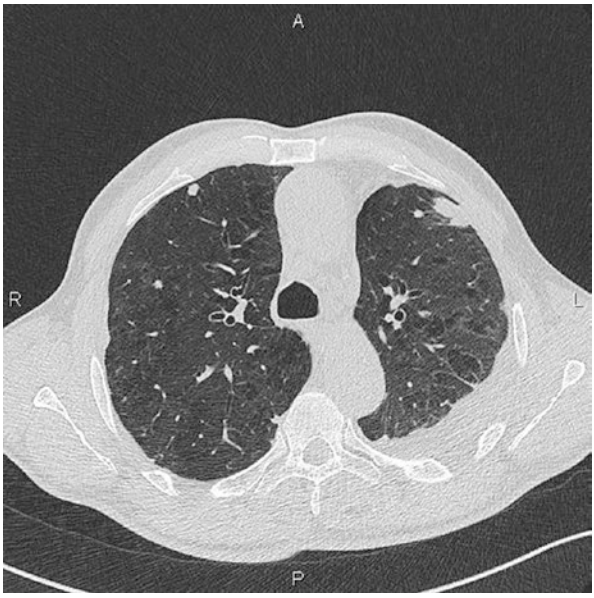

Fig. 9.70 Pneumoconiosis: reticulations in subpleural space, small nodules, fluidothorax on the left, centrilobular emphysema

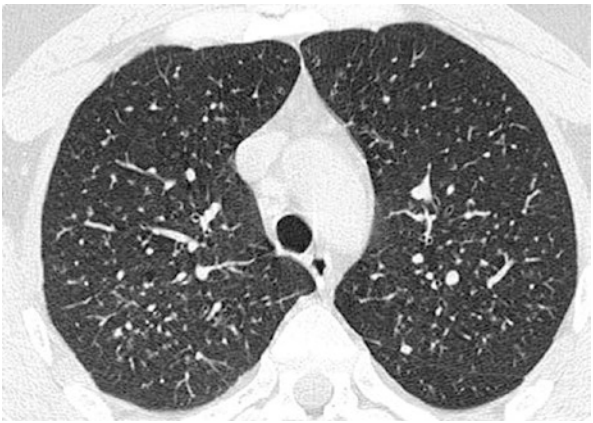

Fig. 9.71 TB: tree-in-bud patterns

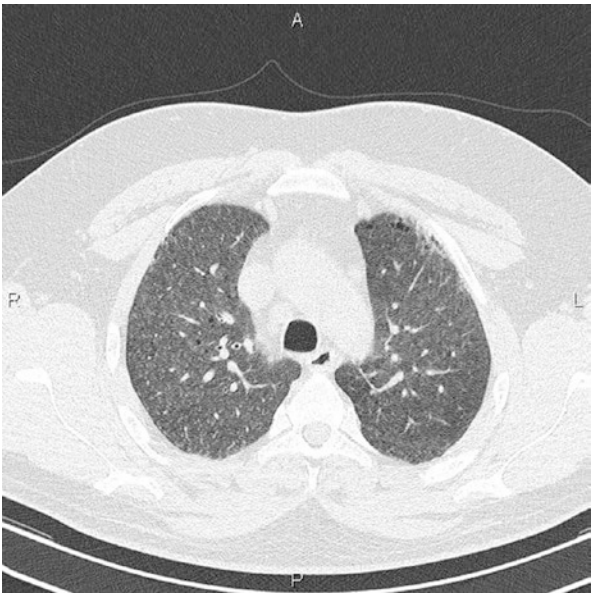

Fig. 9.72 Acute HP: centrilobular sub-solid nodules

Further Reading

Elicker BM, Jones KT, Naeger DM, Frank JA. Imaging of acute lung injury. Radiol Clin N Am. 2016;54:1119–32.

Krause ML, Cartin-Ceba R, Specks U, Peikert T. Update on diffuse alveolar hemorrhage and pulmonary vasculitis. Immunol Allergy Clin North Am. 2012;32:587–600.

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