Mediastinal Lymphoma

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Li Xu and Song Zhang

Lymphomas represent different types of lymphoid malignancies and their patterns of clinical behavior and responses to treatments are varied. The prognosis depends on the histologic type, clinical factors, and molecular characteristics.

Lymphoma is the most common cause of anterior mediastinal mass in children, accounting for 50% of all mediastinal tumors, and the second most common cause in adults. In adulthood, lymphoma accounts for about 20% of anterior mediastinal masses, which is a lower percentage than thymoma that usually affects older patients. In 5% of cases, the anterior mediastinum is the only site of disease (primary mediastinal lymphoma); in these cases, lymphoma may present as isolated thymic involvement, that usually appears as a diffuse thymic enlargement, as isolated nodal involvement, with single or multiple masses, or as a combination of both.

5.1 Classification

Lymphoma can present with either lymphadenopathy or extranodal involvement. They are classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) and further subdivided according to the histologic types. HL accounts for 10–15% of lymphoma and is characterized by the presence of Reed–Sternberg cells. 80–85% of lymphoma is caused by NHL, including B-cell NHLs (B-NHLs) expressing CD20 or CD19, T-cell NHLs (T-NHLs) expressing CD3, CD4, or CD8, and natural killer (NK)/T-cell NHLs expressing CD56. Tumors of mature histiocytic and dendritic cells do not originate from lymphoid cells but often involve lymphoid tissue and historically have been discussed along with mature lymphoid neoplasms.

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5.2 Clinical Features

Intrathoracic involvement is commoner in HL than in NHL. Approximately 85% of patients with HL and 40–45% of patients with NHL have intrathoracic disease at the initial presentation. Most patients with HL are asymptomatic, and systemic symptoms identified as category B of Ann-Arbor staging system are found in only 20–30% of cases at presentation. However, patients with bulky masses may have local symptoms such as chest pain, dyspnea, cough, and dysphagia. Conversely, nearly all patients with NHL have local symptoms, such as respiratory distress and superior vena cava syndrome, as NHLs commonly appear as large anterior mediastinal masses, compressing the airway and cardiovascular structures.

5.3 Radiographic Features

Imaging has played an indispensable role in the initial staging and surveillance of lymphoma, mainly by using CT to detect the disease site and monitor the morphological changes after treatment. The imaging features of primary mediastinal lymphoma are as follows: (1) The masses mostly located in the anterior mediastinum and often directly involve the large vascular space, especially the middle mediastinum vascular space. (2) The masses are rarely confined to one area and often grow around the aortic arch. (3) Mediastinal lymphomas are mostly manifested as huge anterior mediastinal masses accompanied with fused (Fig. 5.1) or isolated (Fig. 5.2) lymph nodes; some patients also have enlarged lymph nodes in the hilum, axilla, or neck. As the most common lymphoma presenting with mediastinal lymphadenopathy, HL most frequently involves lymph nodes in anterior mediastinal and paratracheal areas in a contiguous manner (Fig. 5.3). Therefore, lymph nodes in the hilar, subcarinal, paraesophageal, peridiaphragmatic, and internal mammary areas are involved (Fig. 5.4). Nodes in the anterior mediastinal and paratracheal areas are still the most common sites for

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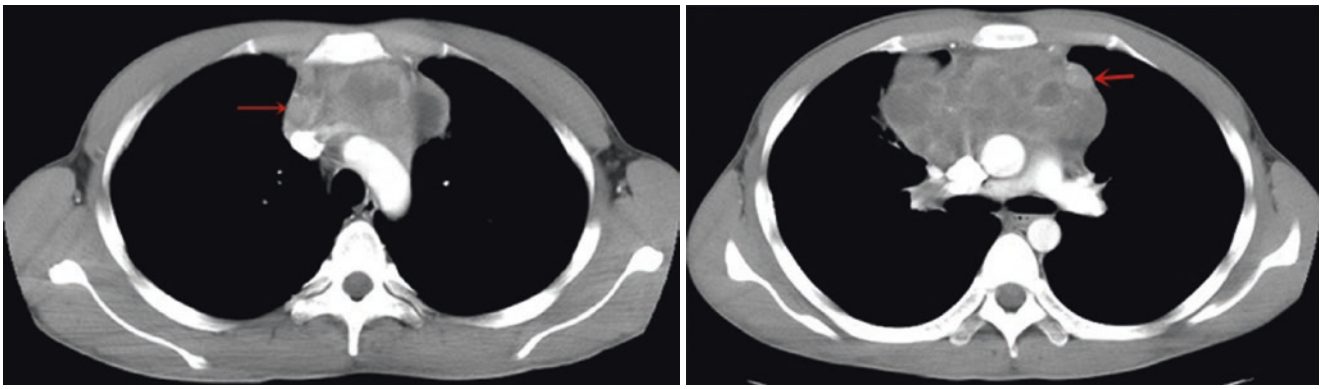

Fig. 5.1 A 30-year-old man with nodular-sclerosis classic HL. Enlarged lymph nodes (red arrows) can be seen around the mass

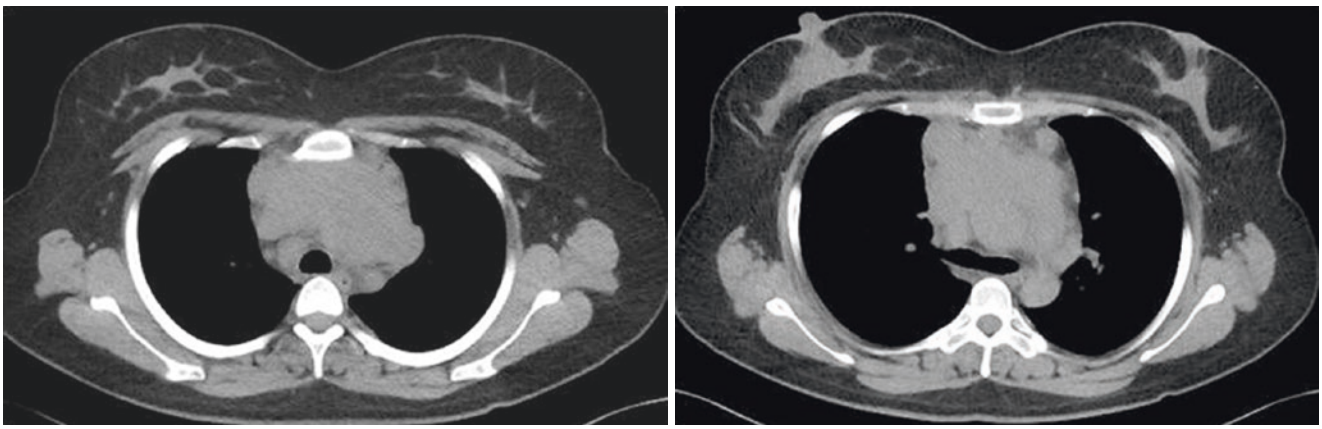

Fig. 5.2 A 24-year-old woman with mediastinal large B-cell lymphoma with multiple isolated lymph nodes around the mass

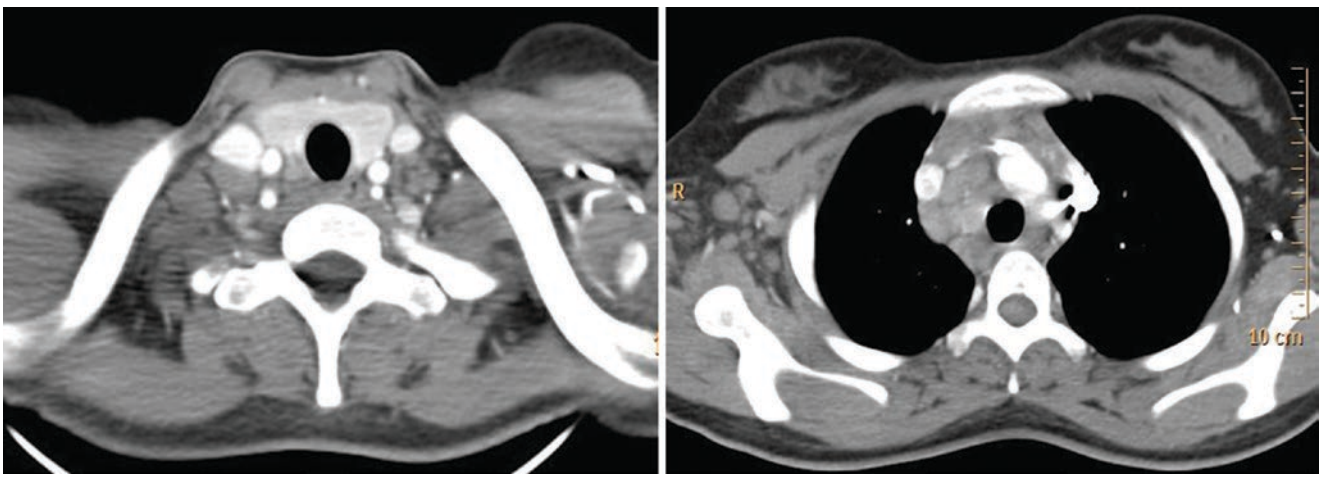

Fig. 5.3 A 20-year-old woman with nodular-sclerosis classic HL. Enlarged lymph nodes can be seen in the cervical, prevascular, axillary, and paratracheal areas

NHL involvement followed by those in the subcarinal, hilar, posterior mediastinal (para-aortic, paravertebral, and retrocrural), and pericardial areas (Fig. 5.5). It is difficult to distinguish HL from NHL on the basis of nodal distribution alone. (4) The heart and large blood vessels are significantly pushed backward and displaced by the mass (Fig. 5.6). (5) The masses often invade the superior vena cava and the left brachiocephalic vein (Fig. 5.7). (6) The masses are irregular, lobulated, and mild or moderate enhancement. The enhancement amplitude of the CT attention is less than 30 HU

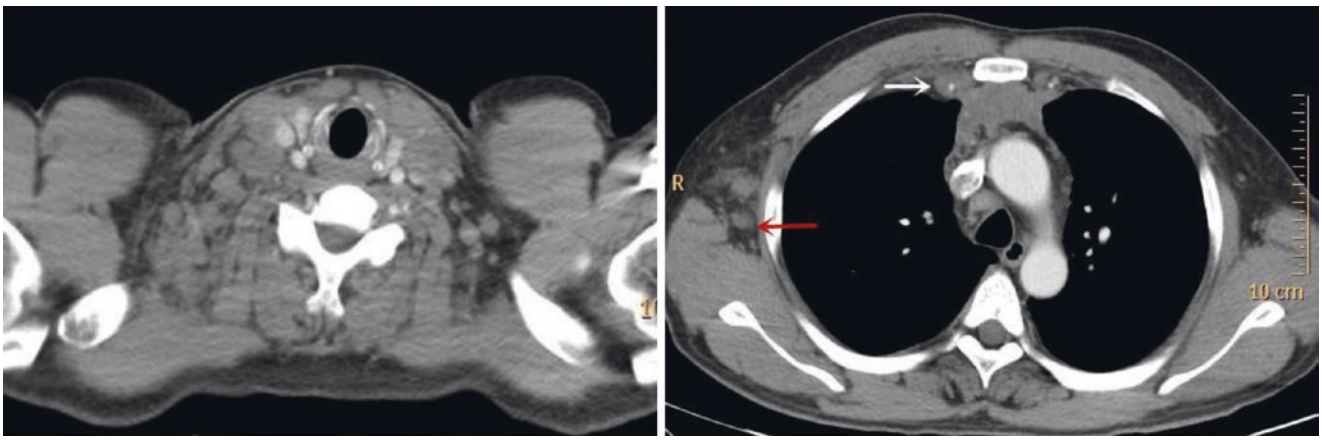

Fig. 5.4 A 41-year-old man with lymphocyte-depleted classic Hodgkin lymphoma. Enlarged lymph nodes can be seen in the cervical, axillary (red arrow), and internal mammary areas (white arrow)

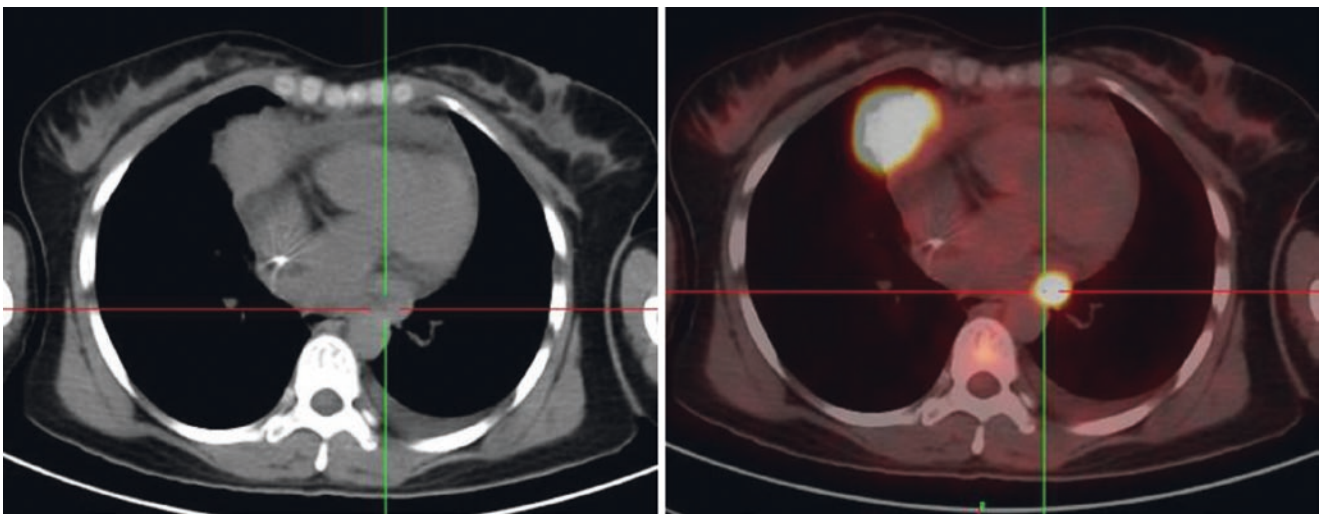

Fig. 5.5 A 30-year-old woman with mediastinal large B-cell lymphoma. Enlarged lymph nodes can be seen in the pericardial area

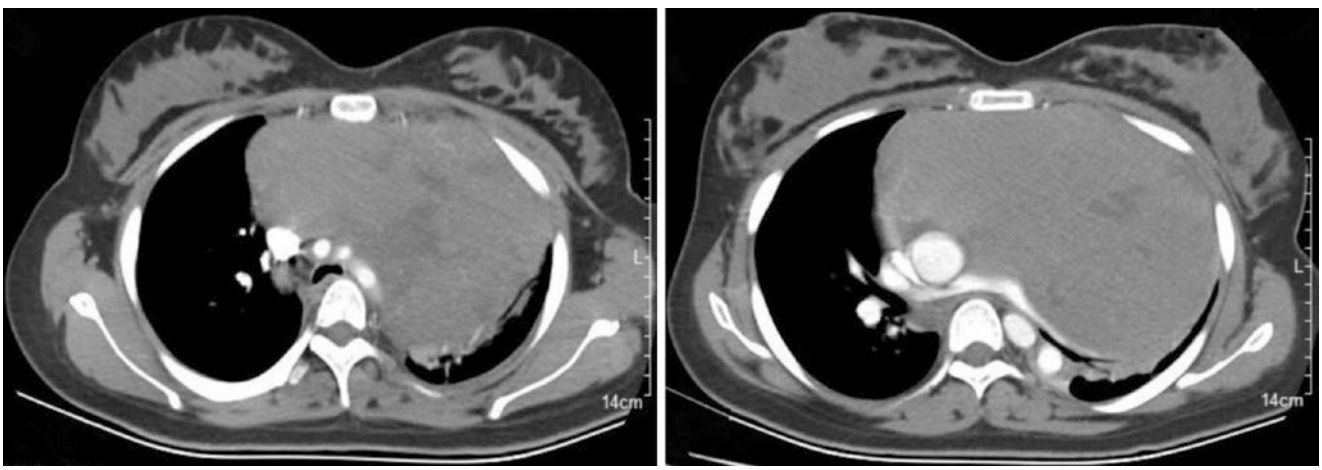

Fig. 5.6 A 23-year-old woman with mediastinal large B-cell lymphoma

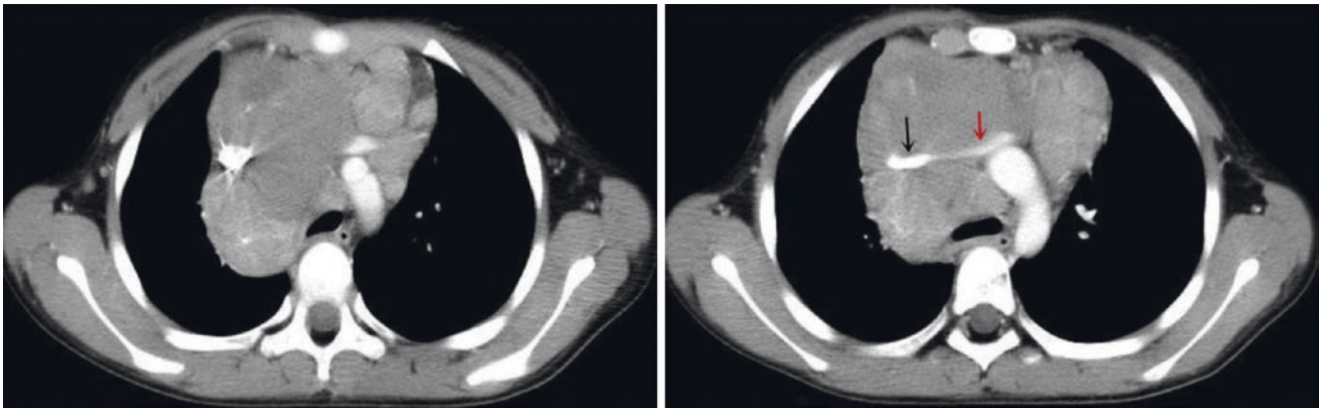

Fig. 5.7 A 9-year-old girl with mediastinal lymphoma, invading superior vena cava (black arrow), and left brachiocephalic vein (red arrow)

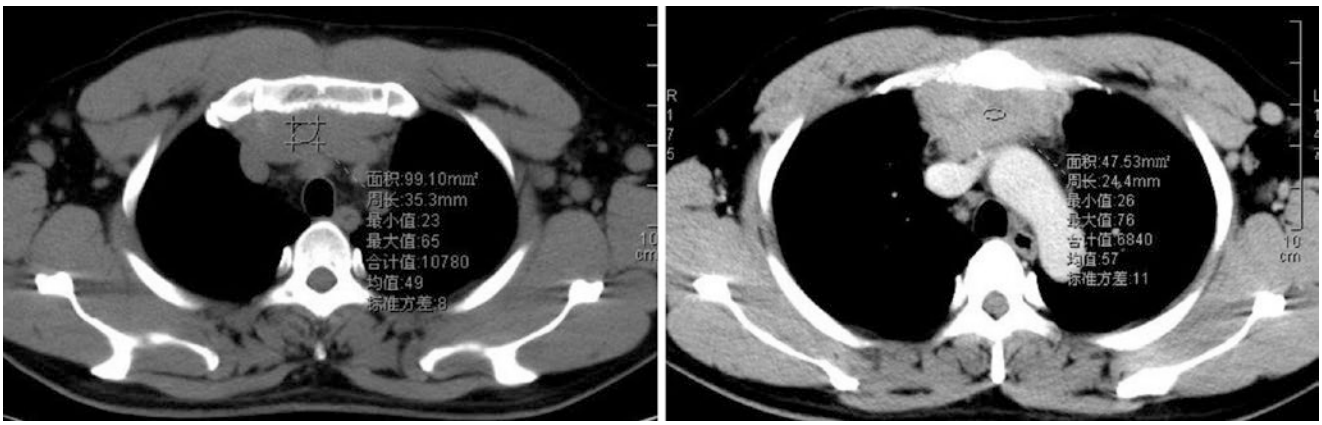

Fig. 5.8 A 40-year-old man with mediastinal large B-cell lymphoma with mild enhancement

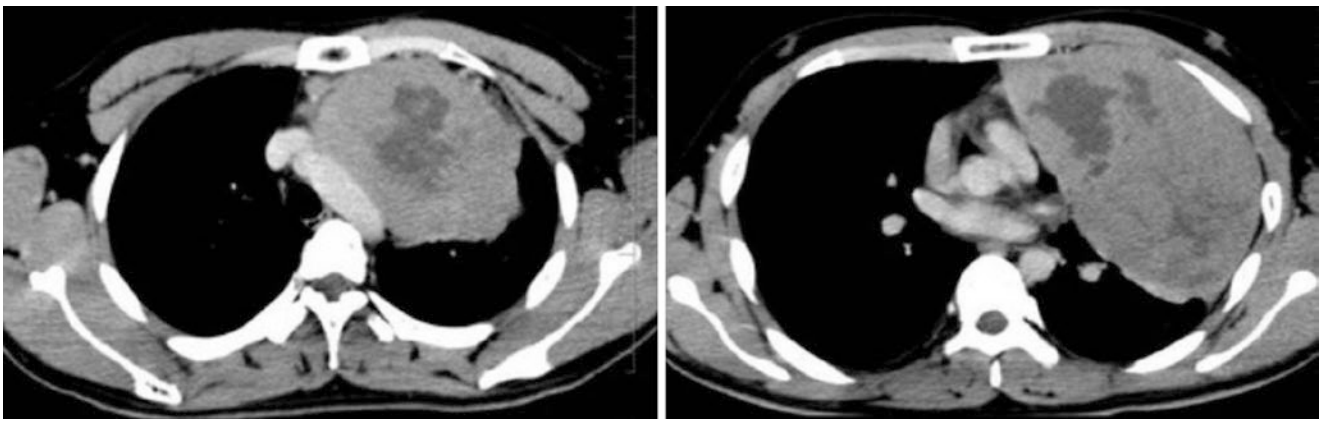

Fig. 5.9 A 23-year-old man with mediastinal large B-cell lymphoma with necrotic or cystic components

(Fig. 5.8). The reason is that most of the anterior mediastinal lymphomas are originated from the thymus and primary thymic lymphomas have less stromal components and less blood supply. (7) Mediastinal lymphomas often demonstrate heterogeneity with complex low attenuation representing necrosis, hemorrhage, or cystic degeneration. This margin of cystic change is clear (Fig. 5.9), which is rare in other anterior mediastinal tumors. (8) Calcification is rare in untreated lymphoma (Fig. 5.10), and about 1% lymphoma can appear calcification after treatment. (9) Mediastinal lymphoma may be associated with pleural and pericardial effusion (Fig. 5.11), but pleural and pericardial nodules are rare. (10) Mediastinal lymphoma can invade the adjacent chest wall and cause bone destruction, forming a large soft tissue mass (Fig. 5.12).

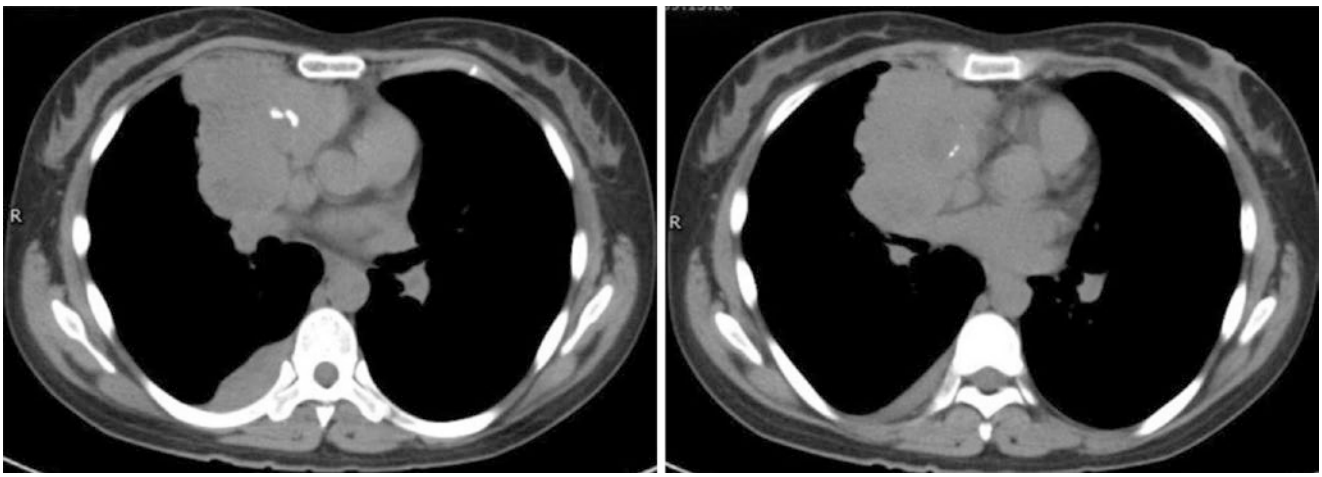

Fig. 5.10 A 28-year-old woman with mediastinal lymphoma with calcifications

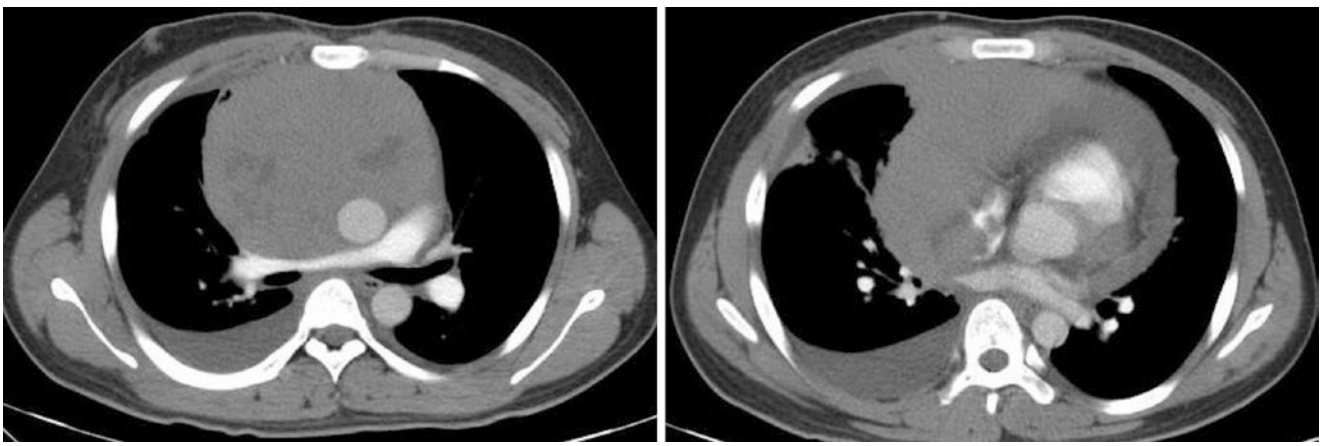

Fig. 5.11 A 17-year-old man with T-cell lymphoblastic lymphoma with pleural and pericardial effusion

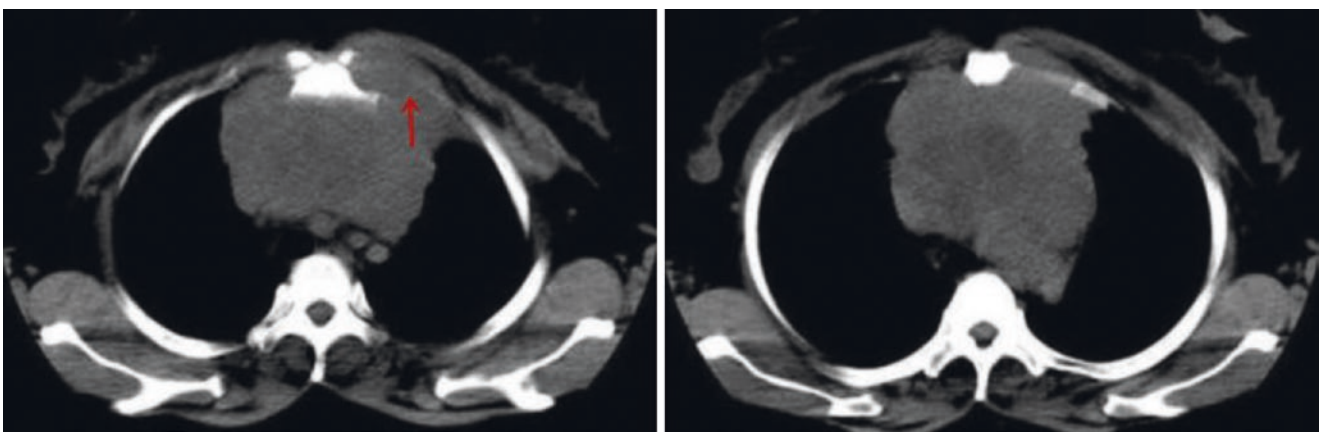

Fig. 5.12 A 34-year-old woman with NHL, invading the adjacent chest wall and forming a mass (red arrow)

5.4 Treatment

There is no optimal first-line treatment of primary mediastinal lymphoma at present. The comprehensive treatment modes including chemotherapy with rituximab (R-CHOP or R-CHOP-like regimen) combined with radiotherapy are used. The annual survival rate is more than 50%. Many factors affect the prognosis of primary mediastinal lymphoma, including behavioral status, remission at initial treatment, male, advanced stage, large mediastinal mass, elevated LDH, and pleural effusion.

5.5 Case Analysis

5.5.1 Case 1

A 37-year-old man complained of chest pain for 1 week.

Chest CT: An irregular mass in the anterior mediastinum, formed by the fusion of several lymph nodes (Fig. 5.13).

[Diagnosis] Mediastinal Hodgkin lymphoma

[Diagnostic basis] A young man with an anterior mediastinal mass, which is formed by the fusion of several lymph nodes, and several enlarged lymph nodes are seen in the supraclavicular area, supporting the diagnosis of Hodgkin lymphoma. Pathology showed nodular-sclerosis classic HL with thymic hyperplasia in some areas. Immunohistochemistry demonstrated positivity for CD30, CD15, CD20, CD3, CD79a, CD21, and PAX-5, and negativity for ALK and EMA.

[Analysis] The term "Hodgkin's disease," now renamed as Hodgkin lymphoma, was first coined by Samuel Wilks, in recognition of the earlier report by Thomas Hodgkin from the Guy's hospital in London (Hodgkin, 1832). Most Hodgkin lymphomas (HL) are of mature B-cell origin, which has been divided into two categories: classic Hodgkin lymphoma (CHL), which accounts for 95% of all HL cases, and the rare nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Worldwide, CHL accounts for 0.5% of all new cancer diagnoses (about 80,000 patients). According to the morphological characteristics of the Hodgkin Reed–Sternberg cells (lacunar cells, multinucleated giant cells, and pseudosarcomatous cells) and the composition of the reactive infiltrate, CHL is distinguished into four histological subtypes: lymphocyte-rich classic Hodgkin lymphoma (LRCHL), nodular-sclerosis CHL, mixed-cellularity CHL, and lymphocyte-depleted CHL. Nodular-sclerosis CHL is the commonest subtype.

Hodgkin lymphomas have four features. They usually arise in the cervical lymph nodes; Hodgkin lymphomas are more common in young adults; there are scattered large mononuclear Hodgkin and multinucleated cells (Reed–Sternberg) intermixed in a background of a mixture of non-neoplastic inflammatory cells; T lymphocytes are often observed around the characteristic neoplastic cells. Hodgkin lymphoma has an excellent overall prognosis, with a cure rate of about 80%.

CHL is a malignancy of germinal center B cells and is characterized by the pathognomonic Hodgkin and Reed–Sternberg cells, which have lost their normal B cell surface markers. Contrary to other B cell lymphomas, the tumor microenvironment is mainly composed of immune effector cells, including cytotoxic T cells and tumor-associated macrophages with a low abundance of malignant B cells. Alteratings in signaling pathways, major histocompatibility complex expression and epigenetic silencing all play a role in pathogenesis, and in some cases Epstein-Barr virus may be present. CHL follows a bimodal age distribution, most patients are diagnosed between the ages of 15 and 30 years, with a second peak in adults older than 55 years. Most patients with CHL have lymphadenopathy. The commonly involved nodal sites include cervical, mediastinal, supraclavicular and axillary, and different subtypes have different site preferences. Classical studies have shown that the spread of disease followed the physiological direction of lymphatic flow; therefore, peripheral non-axial lymph node groups, such as mesenteric or epitrochlear lymph nodes, are rarely involved. Extranodal involvement is usually caused by hematogenous dissemination, and primary extranodal disease is rare. Lung, liver, and bone are the most commonly involved extranodal sites. Patients are often asymptomatic at presentation or have nonspecific symptoms, such as fatigue, cough, severe pruritus, and B symptoms. Patients with EBV, HIV, solid organ transplants, and autoimmune diseases have a higher disease predisposition.

On CT, characteristic features of HL included irregular contour of the anterior mediastinal mass and high prevalence of associated mediastinal lymphadenopathy. The tumor often exhibits homogeneous soft-tissue attenuation, although large lymph node masses may demonstrate heterogeneity with complex low attenuation, representing hemorrhage, necrosis, or cystic degeneration. Hopper et al. [1] found that 21% of cases of HL presented necrotic and cystic changes in mediastinal lymph nodes. Necrosis is observed most commonly in the nodular-sclerosis and mixed-cellularity types of HL and was not seen in the lymphocyte-predominant variety. Pulmonary involvement is identified more often in HL than in NHL. CT findings of HL showed the absence of vascular involvement. Pleural effusions are observed in approximately 10% of patients in HL. Pleural effusions are usually caused by lymphatic or venous obstruction by enlarged lymph nodes rather than directly caused by lymphomatous involvement. The fluid can be serous, pseudochylous, chylous, or rarely serosanguinous.

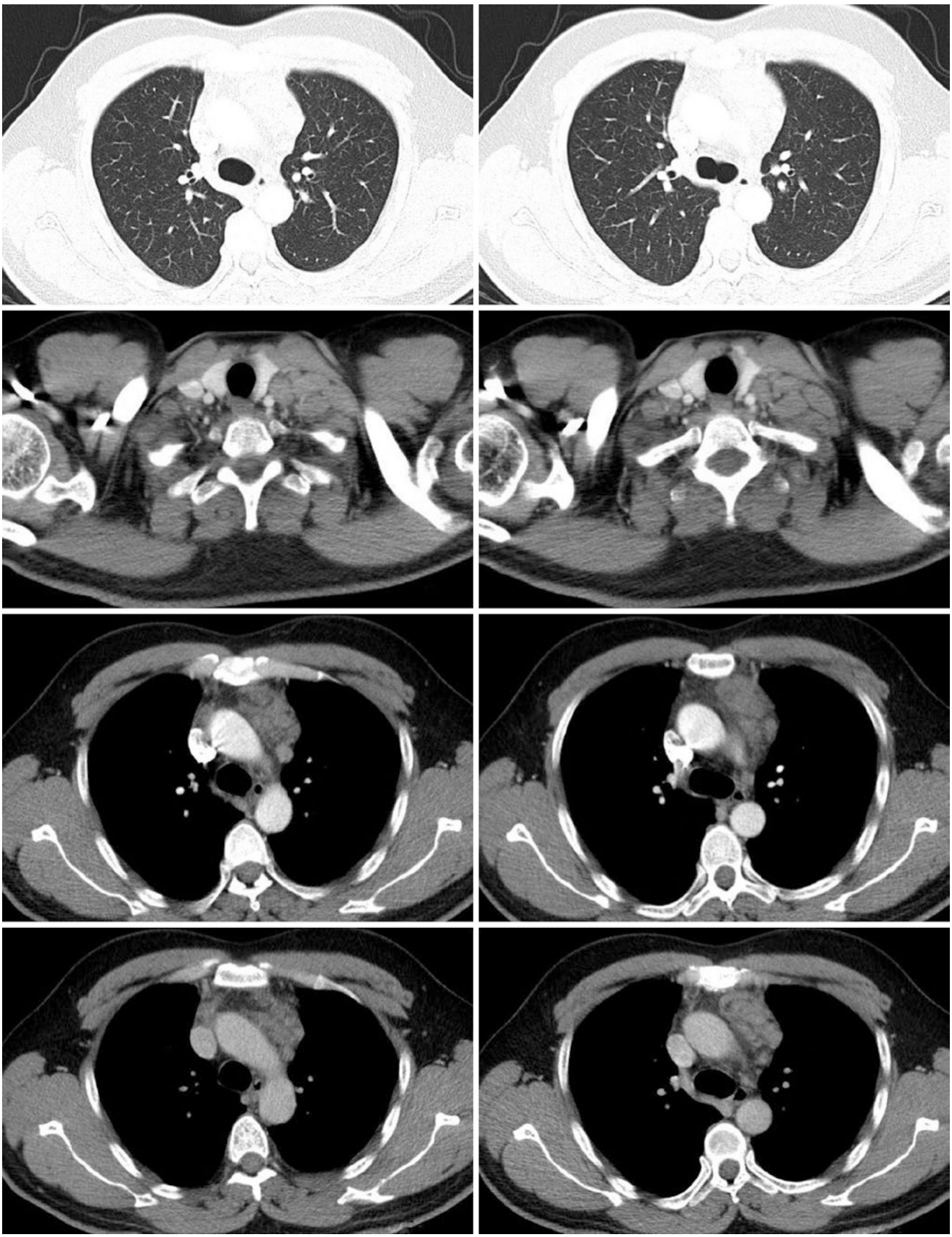

Fig. 5.13 Chest CT images of a 37-year-old man complained of chest pain for 1 week

In the past 50 years, with the emergence of effective multidrug chemotherapy combinations, with or without radiotherapy (RT), HL has been transformed from a highly fatal disease to a highly curable disease. In addition to targeting tumor cells, the nontumor microenvironment also provides important therapeutic targets with clinical implications.

In localized stages without adverse prognostic factors (early stages), brief courses (two to three cycles) of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy followed by involved-field or involved-node radiotherapy (IFRT, INRT) can produce very satisfactory results, with indicative 10-year progression-free survival (PFS) and 10-year overall survival (OS) rates of 87% and 94%, respectively. In localized stages with risk factors (intermediate stages), the results are also satisfactory with four cycles of ABVD plus IF(IN)-RT, with PFS and OS of at least 83% and 91% at 10 years, respectively. Two cycles of BEACOPP-escalated plus ABVDx2 and RT intensive treatment can improve disease control, but not OS. Older patients usually do not tolerate combined chemotherapy regimens, but may derive benefit from single agents, such as gemcitabine, and liposomal doxorubicin.

Advanced stage HL has been recently treated with either ABVD or BEACOPP chemotherapy regimens, mainly according to national preferences. Excellent disease control rates have been demonstrated with the more intensive BEACOPP regimens, but at the cost of more acute toxicity and long-term morbidity.

Depending on the choice of first-line therapy, about 10–15% of patients with early-stage HL and 15–30% of patients with advanced stage tumor will have primary refractory lymphoma or experience recurrence. High-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) is administered infeasible and can result in long-term remission in up to 50% of cases.

For those patients who are chemotherapy refractory, relapse after, or are ineligible for ASCT, brentuximab vedotin (BV), and the checkpoint inhibitors (nivolumab and pembrolizumab) are highly active, although the majority of patients will ultimately experience recurrent lymphoma. BV is an antibody–drug conjugate that binds to CD30 antigen and is able to give up to 34% metabolic complete remissions (mCR) in HL patients that fail auto-HCT. The release of the immune system with PD-1 inhibitors has resulted in significant responses in a number of malignancies, including HL. Nivolumab and pembrolizumab provide a 20–25% mCR and 40–50% partial remissions, with an acceptable safety profile. As well as early approaches with chimeric antigen receptor (CAR) T cells, other new drugs under investigation include Janus kinase 2 (JAK2) inhibitors, histone deacetylase (HDAC) inhibitors, and immunomodulators.

The helpful combination of these different drugs will eventually improve not only the mCR rate, but also PFS, and will eventually translate into the long-term curability of these patients.

5.5.2 Case 2

A 34-year-old woman complained of chest tightness and chest pain for a month.

Chest CT: An anterior superior mediastinal mass with multiple enlarged lymph nodes in the mediastinum, invading blood vessels and pericardium (Fig. 5.14).

[Diagnosis] Primary mediastinal large B-cell lymphoma

[Diagnosis basis] Contrast-enhanced CT images show a heterogeneous anterior mediastinal mass with irregular contours, calcification (black arrow), a mild degree of enhancement, and necrotic or cystic components (blue arrow); the mass invade superior vena cava (red arrow) and lymph node (white arrows)adjacent the pericardium, the above features support the diagnosis of non-Hodgkin's lymphoma, especially large B-cell lymphoma. The final pathological diagnosis was mediastinal large B-cell lymphoma. Immunohistochemistry demonstrated positivity for LCA and CD20. The staining index for Ki-67 was about 80%.

[Analysis] Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL in adults and includes a heterogeneous group of tumors that differ at the clinical, pathological, molecular, and biological levels. Several subtypes of DLBCL have been designated as distinct entities in the WHO classification, including primary DLBCL of the central nervous system; primary cutaneous DLBCL, leg type; T-cell/histiocyte-rich LBCL; intravascular LBCL; Epstein–Barr virus (EBV)-positive DLBCL; and DLBCL associated with chronic inflammation. The remaining DLBCLs are classified as DLBCL, not otherwise specified (NOS).

Gene expression profiling (GEP) studies have revealed two different molecular forms of DLBCL corresponding to different stages of B-cell differentiation: germinal center B-cell-like (GCB) DLBCL is associated with a better prognosis, and activated B cell-like (ABC) DLBCL is associated with a worse prognosis. Based on historical data, the 5-year overall survival rate in patients with GCB DLBCL was 76% compared to 34% for non-GCB DLBCL.

Primary mediastinal large B-cell lymphoma (PMBCL) was first reported in 1980s and was incorporated in the Revised European–American Lymphoma classification in 1994. In 2008, the WHO classification of hematopoietic and lymphoid tissues tumors also regarded PMBCL as an independent entity under mature B-cell lymphomas. PMBCL is an uncommon subtype of DLBCL that has molecular simi-

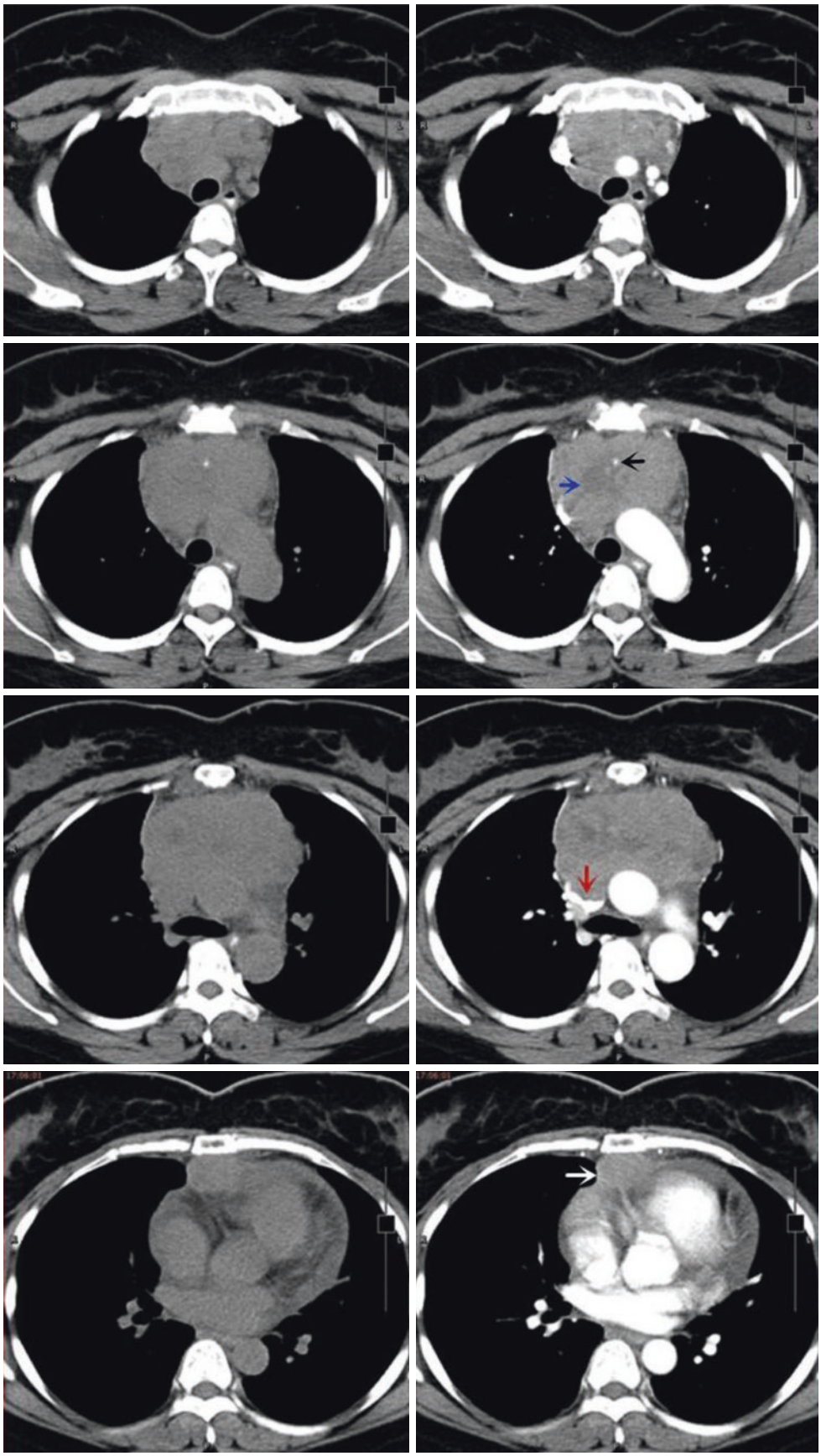

Fig. 5.14 Chest CT images of a 34-year-old woman complained of chest tightness and chest pain for a month

larities to nodular-sclerosis CHL. PMBCL makes up 2–4% of all NHLs and 6–12% of all DLBCLs. It occurs predominantly in the third or fourth decade of life and has a slight female predominance, particularly in white patients.

Clinically, PMLBCL usually presents as a rapidly expanding mediastinal mass leading to oppressive respiratory symptoms. Common presenting symptoms include cough, chest pain, hoarseness, dyspnea, dysphagia, and B symptoms such as fevers, chills, weight loss, and night sweats. Up to 80% of cases show elevated lactate dehydrogenase (LDH) and approximately one-third of cases can present with superior vena cava (SVC) syndrome, pleural effusion, or pericardial effusion. Enlarged supraclavicular lymph node is less common on initial presentation but occurs more frequently at recurrence.

The Ann Arbor staging system is used in approximately 75% of patients present with stage I or II disease, and most patients will present with a bulky (≥10 cm) mediastinal mass. There is often intrathoracic extension to adjacent organs including the chest wall, pleura, lungs, pericardium, and heart. The mass tends to be confined to the thorax without the involvement of lymph nodes or other lymphoid organs at initial diagnosis. Extra-thoracic or extra-nodal involvement is more frequent at relapse and may involve liver, gastrointestinal tract, kidneys, and ovaries. Bone marrow involvement is uncommon and observed in 1–5% of cases. Central nervous system (CNS) involvement, in the form of leptomeningeal or intraparenchymal disease, is uncommon and seen particularly with extranodal disease and at relapse.

5.5.3 Case 3

A 40-year-old woman's physical examination revealed a mediastinal mass.

Chest CT: An anterior superior mediastinal lesion that invaded the anterior chest wall. The solid part of the mass was mild to moderate enhancement with central low-density non-enhanced areas. Enlarged lymph nodes can be seen in the right armpit (Fig. 5.15).

[Diagnosis] Anterior mediastinal lymphoma

[Diagnostic basis] Incompletely fused lymph nodes (red arrows) can be seen adjacent to the anterior superior mediastinal mass. A contrast-enhanced scan shows large non-enhanced areas with clear boundaries, combined with the patient's age, supporting the diagnosis of lymphoma. Intraoperatively, the tumor capsule was intact. Microscopically, the tumor cells were large and diffusely arranged, and mitosis was easy to see. Immunohistochemistry

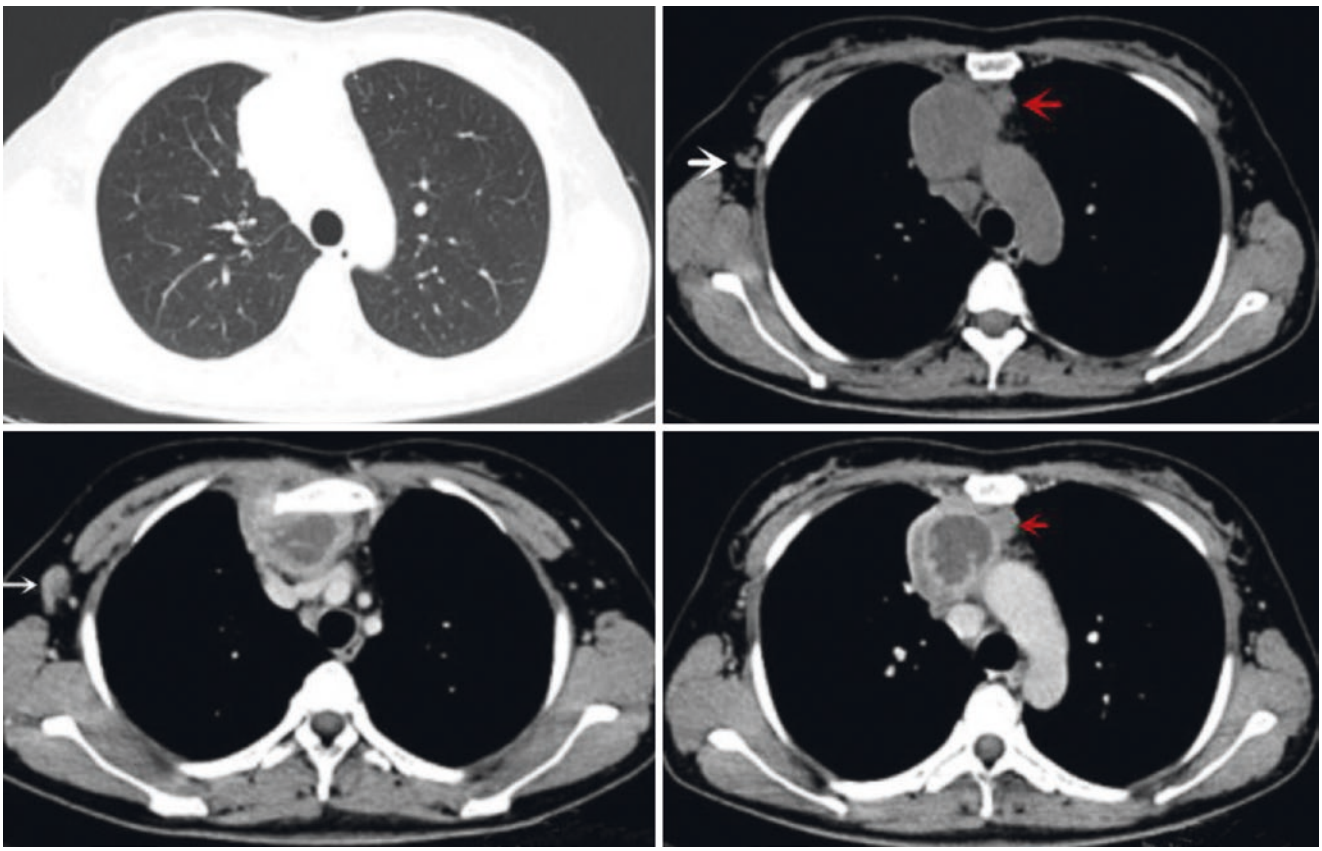

Fig. 5.15 Chest CT images of a 40-year-old woman's physical examination revealed a mediastinal mass

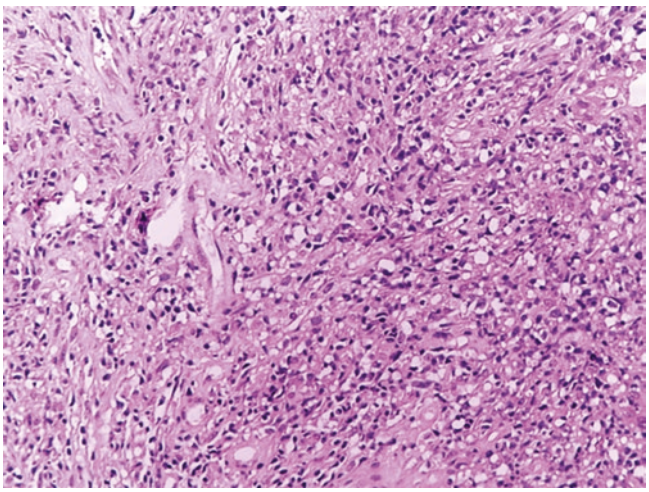

Fig. 5.16 Pleomorphic tumor cells with abundant pale cytoplasm and marked stromal fibrosis

demonstrated positivity for CD20 and CD45RO, and negativity for TdT, CD3, CK, and EMA. Axillary lymph nodes (white arrow) were found to have cancer nests with papillary and adenoid cells. Combined with pathology and immunohistochemistry, it was considered as thymic and mediastinal large B-cell lymphoma (Fig. 5.16); metastatic carcinoma of axillary lymph nodes (papillary adenocarcinoma), which was recommended to check the breast, thyroid, lung, etc.

[Analysis] When anterior mediastinal lymphoma was centrally located, the diagnosis is not difficult. When the mass is relatively on one side, especially when it involves the thymus, it is easy to be misdiagnosed as thymoma. In this case, the enlarged axillary lymph node is papillary adenocarcinoma, which further shows that PMBL hardly invades the axillary lymph nodes.

PMLBCL is considered to typically arise from a small population of B cells within the thymus and thymic components such as Hassall corpuscles may be identified in the pathology specimen. On comparative genomic hybridization, PMBCL often demonstrates gain in chromosome 9p and 2p14–p16. Amplification of the 9p24.1 region is a disease-specific structural alteration, which not only increases the gene dosage of programmed cell death ligand-1 (PD-L1), but also includes the Janus kinase 2 locus (JAK2). Protein expression and activity were increased by JAK2 amplification, which specifically induced PD-L1 transcription and enhanced sensitivity to JAK2 inhibition. These aberrations are thought to affect tumor–microenvironment interactions resulting in immune privilege. The tumor hallmark of immune privilege is mainly supported by downregulation of MHC class I and II molecules and overexpression of PDL leading to reduced immunogenicity and T cell energy. Loss of MHC molecules, in particular, MHC class II has been described as a common feature in PMBCL. Recent work has identified PMLBCL disease biology as dependent on molecular pathways involving REL, JAK-STAT, PD-L1/PD-L2, and nuclear factor κβ (NF-κβ). Gene expression profiling has confirmed these findings and demonstrated a closer relationship between PMBCL and HL than with typical DLBCL.

Morphologically, PMBCL is composed of large centrocytes and medium centroblasts with abundant pale cytoplasm. Occasionally, some cells are multinucleated and resemble Reed–Sternberg cells of HL. Fibrosis is another characteristic feature. The infiltrating cells are often entrapped in compartments surrounded by collagenous fibrosis, forming so-called compartmentalizing alveolar fibrosis.

Immunohistochemically, PMBCL expresses the mature B-cell antigens CD19, CD20, and CD79a, and nuclear transcriptional regulators such as BOB1, PU.1, OCT2, PAX5, BCL6, and IRF4. However, it usually does not express surface immunoglobulins like other DLBCLs. It has variable expression of BCL2 and BCL6, and in contrast with other subtypes of DLBCLs, BCL2, BCL6, and MYC genes rearrangements are usually absent. Although the thymus is responsible for the maturation of T-cells, it also has a B-cell population around Hassall's corpuscle with unique characteristics including expression of CD19, CD20, CD22, IgM, and absence of CD21. PMBCL cells are positive for CD19 and negative for CD21, indicating the origin of thymic B-cell, which is also supported by the presence of remnants of thymus within the tumor mass. PMBCL is weakly positive for CD30, which is a marker observed in CHL, but CD15 is usually absent. PMLBCL is usually negative for the expression of CD3, CD10, and class I/II major histocompatibility antigens. These markers collectively support the concept that many of these lymphomas are from activated germinal center or post-germinal center reaction cells, and despite the expression of transcription factors, they are distinct from similar lymphomas due to the lack of surface immunoglobulin.

The differential diagnoses of PMBCL include other types of mediastinal regional lymphoma and mediastinal tumors such as germ cell tumors, thymoma, and metastatic carcinomas. The most mimicking tumor of PMLBL is thymic neoplasm (thymoma and thymic carcinoma). The expression pattern of pancytokeratin is useful to differentiate them and highlights overlying and entrapped thymic epithelium in thymic tumor. In germ cell tumor, β-HCG and α-fetoprotein in serum are increased, and immunohistochemistry is positive. PMBCL highlights an overlap with the nodular sclerosis subtype of CHL sharing a number of genetic and gene expression features. Surface immunoglobulin expression is usually absent in both types of lymphomas. Marked stromal fibrosis and the presence of tumor cells which looked like Reed–Sternberg cells with bilobed nuclei mandate the exclusion of HL. Additionally, as mentioned previously, PMBCL commonly expresses CD30, although weaker and more heterogeneously than CHL. CD15 negativity can also exclude HL.

5.5.4 Case 4

A 47-year-old woman complained of cough and sputum for 2 weeks.

Chest CT: Anterior mediastinum mass with slight enhancement and cystic change, invading superior vena cava. Enlarged lymph nodes could be seen in the cervical and axillary areas (Fig. 5.17).

[Diagnosis] Mediastinal large B-cell lymphoma

[Diagnosis basis] Mediastinal mass biopsy showed that tumor cells were detected and large B-cell lymphoma was considered. The R-DA-EPOCH regimen was used for 2 cycles, and the lesion was significantly reduced (Fig. 5.18).

[Analysis] Although it is very difficult to choose a specific chemotherapy regimen because clinical studies cannot compare similar patient groups, the current standard first-line treatment for PMBCL patients is rituximab-based immunochemotherapy. There are several options, including 6 cycles of R-CHOP-21 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, given every 21 days) with consolidation radiotherapy to the mediastinum, 6 cycles of DA-EPOCH-R (dose adjusted (EPOCH) etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, ritux-

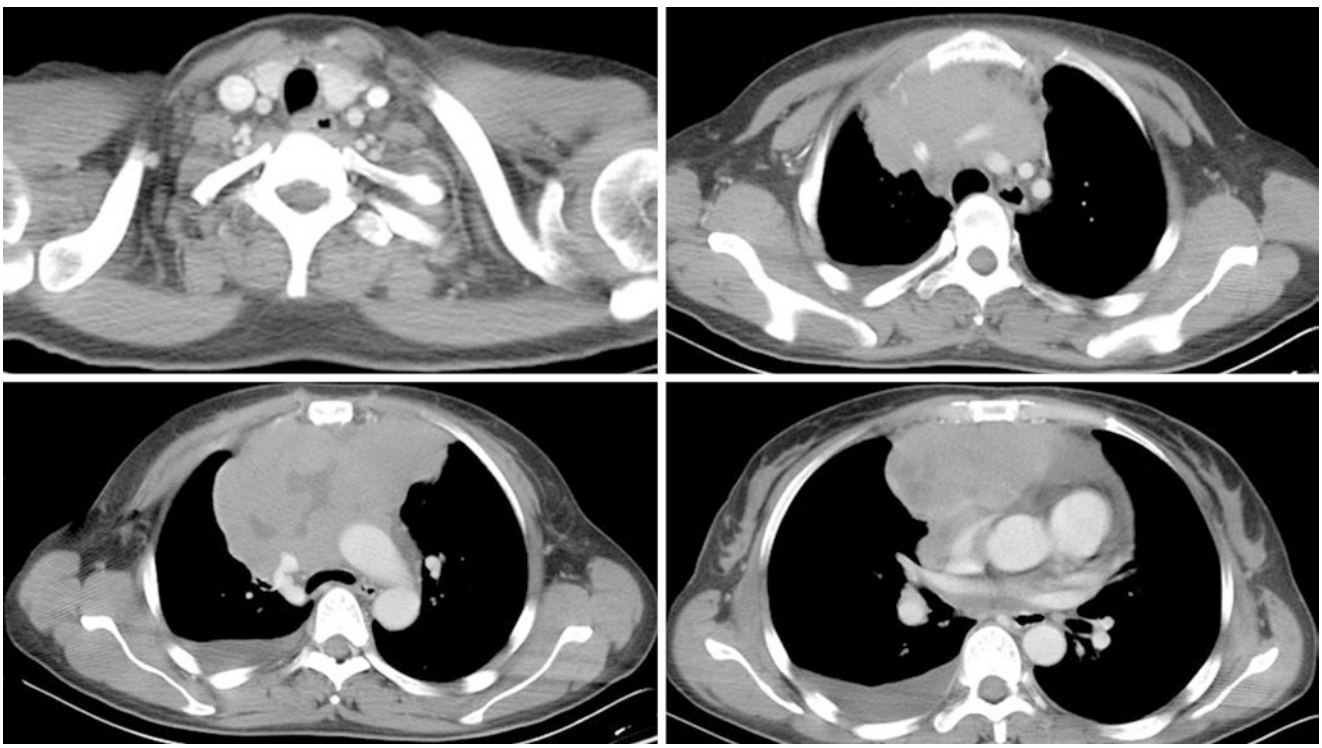

Fig. 5.17 Chest CT images of a 47-year-old woman complained of cough and sputum for 2 weeks

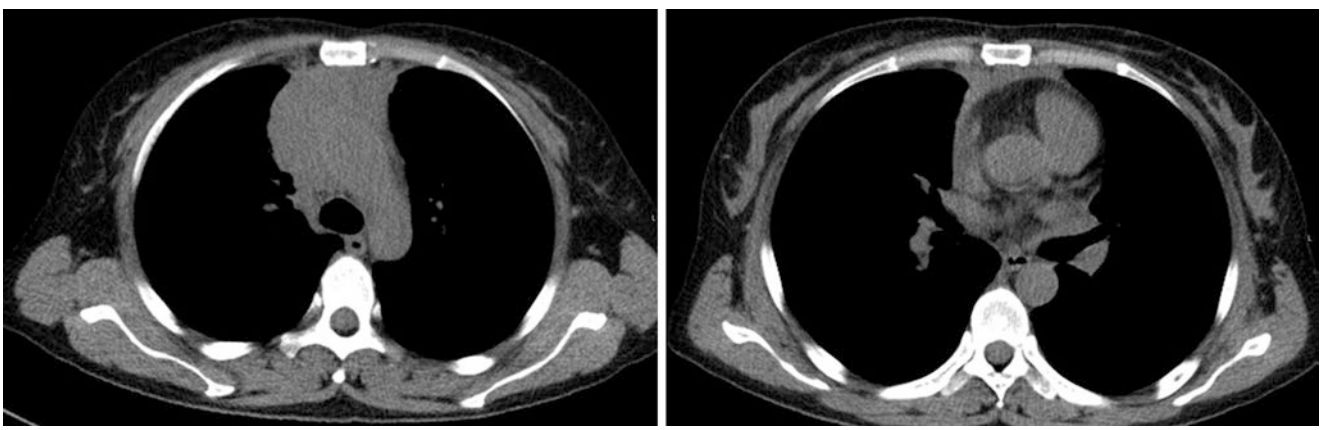

Fig. 5.18 Mediastinal mass was significantly reduced after chemotherapy

imab), 4 cycles of R-CHOP, and 3 cycles of ICE (ifosfamide, carboplatine, etoposide) with possible radiotherapy based on treatment outcomes. In 2013, a prospective phase 2 clinical study of patients with PMBCL treated with DA-EPOCH-R without radiotherapy was reported by Dunleavy et al. [2]. The final analysis included 51 patients (59% of women) with a median age of 30 years. The 5-year event-free survival (EFS) and overall survival (OS) were 93% and 97%, respectively. Generally, patients with PMLBCL who obtain a complete remission (CR) lasting longer than 24 months are likely to be cured. Studies have shown a plateau at the survival curve beyond 24 months. However, usually within 6–18 months after completing therapy, 10–30% of patients may still experience disease progression or relapse after initial treatment. Disease recurrence can be local or more extensive, extending to extranodal sites, such as the liver, kidneys, and ovaries.

The approach to relapsed/refractory PMBCL has been similar to that of relapsed/refractory DLBCL with treatment regimens. Salvage chemotherapy (often with rituximab and radiotherapy), followed by high-dose treatment (HDT) and stem cell transplantation (SCT), appears to be the standard real-world treatment for relapsed/refractory PMBCL. However, the roles of rituximab and mediastinal radiotherapy have yet to be fully elucidated. Allogeneic stem cell transplantation (ASCT) may be considered as an experimental option; nonetheless, generally speaking, if patients with relapsed/refractory PMBCL are not candidates for (or fail to respond to) HDT, the remaining treatment options are largely limited to enrolment in clinical trials and palliative/supportive care.

In the era of new molecular insights of the PMLBCL pathogenesis, novel agents are warranted (PD-L1, PD-L2, JAK2/STAT molecular pathway inhibitors). PMBCL and CHL share many features, including the expression of program PD-L1/2. Pembrolizumab is a PD-1 inhibitor that binds PD-1 and blocks the activation of PD-1 and PD-L1/2 signals. In March 2017, according to the KEYNOTE-087 trial, Pembrolizumab was approved for the treatment of relapsed/refractory CHL with an OR rate of 69%. Some studies have shown OR rates of 41% with pembrolizumab salvage therapy. This is higher than the prior retrospective studies using traditional regimens for DLBCL (DHAP, ESHAP, GDP, and mini-beam), which have shown 0–25% OR rates in relapsed/refractory patients.

Preclinical and clinical studies in both solid tumors and hematologic malignancies have shown that the combination of immune checkpoint inhibitors and immune checkpoint inhibitors combined with other therapeutic drugs may have synergistic effects. In relapsed/refractory HL, the combination of nivolumab with brentuximab vedotin (BV) has shown an OR rate of 82–89% and a CR rate of 50–61%. The OR and CR rates of combination therapy were higher than those of nivolumab or BV alone. Given the high response rates in the relapsed/refractory setting, efforts are being made to improve clinical outcomes by moving immune checkpoint inhibitors to the first-line setting.

The JAK/STAT pathway is another potential therapeutic target in PMBCL. The JAK2 inhibitor, ruxolitinib, and the JAK2/FLT3 inhibitor, SB518, have both been evaluated in HL and PMBCL. However, due to the small number of cases so far, no conclusion has been drawn on its efficacy.

PMBCL is significantly different from other mature B-cell lymphomas and further studies of effective salvage therapies are needed.

5.5.5 Case 5

A 69-year-old woman complained of fever for 45 days. She has a history of Sjögren's syndrome (SjS) for 7 years with dry eyes and dry mouth symptoms. Blood studies showed elevated antibodies positive for ANA at the titer of 1:2560 and SS-A, SS-B, and Ro-52. Serum rheumatoid factor (RF) was elevated to 106 IU/ml (normal range 0–15). Immunoelectrophoresis-serum test showed that IgA and IgG were positive. Complete blood count showed three-line reduction, with a white blood cell count of 1.62×10^3/L. Ultrasound examination revealed enlargement of parotid gland and enlarged lymph nodes in bilateral groin, armpit, and neck.

Chest CT: Anterior mediastinum mass with cystic change and bilateral pleural effusions (Fig. 5.19).

[Diagnosis] Primary mediastinal (thymic) MALT lymphoma

[Diagnosis basis] An old-aged Asian woman has a history of SjS; chest CT revealed a multilocular mediastinal mass without invasion of the surrounding parenchyma; the laboratory data showed nothing but hypergammaglobulinemia. The above features should raise a suspicion of a primary thymic MALT lymphoma as the most likely differential diagnosis. Surgery via a median sternotomy was performed. The tumor originated from the thymus gland and did not invade the surrounding structures and organs. The cut surface showed a grayish-white solid mass with multiple cysts. In histopathology, an infiltration of numerous lymphoid cells with lymphoid follicles was found. Atypical lymphoid cells were observed, and some of them showed plasmacytoid differentiation. Immunohistochemistry demonstrated positivity forCD20, CD21, CD38, EMA, and Lambda, and negative for TdT, CD138, and Kappa. The diagnosis of thymic MALT lymphoma was made.

[Analysis] Mucosa-associated lymphoid tissue (MALT) lymphoma is a type of extranodal marginal zone B cell lymphoma (MZBL) and is a distinct subtype of non-Hodgkin's lymphoma, which was first described by Isaacson and

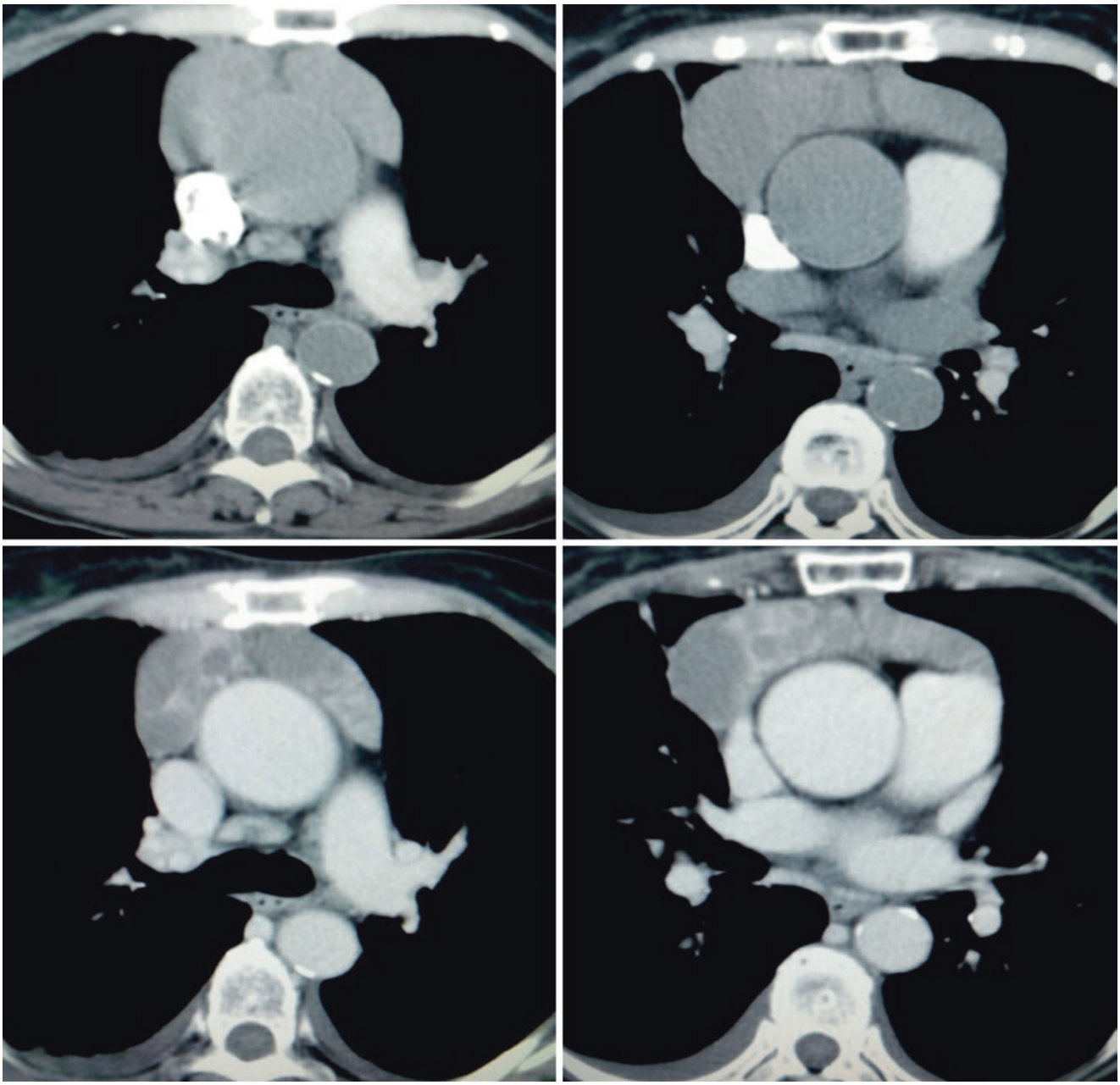

Fig. 5.19 Chest CT images of a 69-year-old woman complained of fever for 45 days

Wright in 1983 [4]. They found that more histological features in common were present in primary low-grade gastric B cell lymphomas and immunoproliferative small intestinal disease and those of mucosa-associated lymphoid tissue than with peripheral lymph nodes. Extranodal low-grade lymphomas arising at other mucosal organs, including the salivary gland, thyroid, and lung, showed similar histological and clinical features, and therefore established the term "MALT lymphoma." MALT lymphomas occurs in a wide range of different extranodal sides, including the stomach (70%), lung (14%), ocular adnexa (12%), thyroid (4%), and small intestine (including immunoproliferative small intestinal disease; 1%).

Approximately 8% of all NHLs are MALT lymphoma. The histological feature of MALT lymphoma comprises infiltration of the marginal zone and spreading diffusely into the surrounding tissue. The lymphoma cells often resemble follicle-center centrocytes, small lymphocytes, or the so-called monocytoid B cells. Another important histological feature is the presence of lymphoepithelial lesions formed by the lymphoma cell invasion of individual mucosal glands or other epithelial structures. Transformed blasts and plasma

cells are scattered, present beneath the surface epithelium, possibly indicating that the MALT lymphoma might participate in the immune response. The lymphoma cells also enter the germinal centers of nonneoplastic B cell follicles—a process known as follicular colonization.

Several chromosomal translocations specific to MALT lymphoma have been identified, including t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), and t(3;14)(p14.1;q32). The former translocation, which is the most frequent, forms the apoptosis inhibitor 2 gene (*API2*)–MALT-lymphoma-associated translocation 1 (*MALT1*) fusion, and the latter three, although rare, form an immunoglobulin heavy (*IGH*) locus gene rearrangement with MALT1, B-cell CLL/lymphoma 10 (*BCL10*), and forkhead box P1 (*FoxP1*), respectively. t(3;14) has been found in a subset of diffuse large B-cell lymphomas, and may not be very specific to MALT lymphomas. In addition, trisomies 3 and 18 are often detected in MALT lymphomas. Important in tumor development, these chromosomal abnormalities may be associated with the distinctive clinicopathological features of MALT lymphoma at various anatomical sites.

Chronic inflammation and autoimmune disease are often associated with the emergence of MALT lymphoma, such as chronic infection by *Helicobacter pylori* in the stomach, *Chlamydia psittaci* in the ocular adnexa, *Borrelia burgdorferi* in the skin, and *Campylobacter jejuni* in the small intestine, as well as autoimmune disorders including Hashimoto thyroiditis and lymphoepithelial sialadenitis. Long-term chronic infection and/or autoimmunity generate active immune and inflammatory responses that provide conditions for evolution and development of autoreactive B-cells, their expansion and eventually malignant transformation following acquisition of genetic changes.

Primary SjS (pSS) patients have a substantially increased risk of malignancy relative to age-matched controls. This includes an especially elevated risk of NHL, such as MALT lymphoma, follicular lymphoma, and diffuse large B cell lymphoma. The lifetime risk of NHL in pSS patients is approximately 5–10%, with pSS patients being at 15–20 times at greater risk compared with the general population. From the diagnosis of pSS, the risk increases with age and time. In the context of chronic antigen stimulation, it is believed that the main factors leading to lymphoma in pSS patients may be aberrant NF-κB production and abnormal BAFF signal. Among patients with pSS, the clinical manifestations most likely to develop into lymphoma include fixed parotid enlargement, vasculitic rashes (such as palpable purpura), higher disease activity, and peripheral neuropathy. Biochemical findings that confer a higher lymphoma risk include low C4, the presence of cryoglobulins, rheumatoid factor positivity, SS-A/B positivity, and neutropenia, among others. The clinical findings of our patient that put her at a higher risk of lymphoma included higher disease activity, fixed parotid enlargement, neutropenia, and SS-A/B positivity.

In 1990, MZBL arising in the thymus gland was defined as thymic MALT lymphoma by Isaacson [5]. Primary thymic MALT lymphomas are prevalent in middle-aged Asian women (approximately 80% of reported cases are Asian patients and the female-to-male ratio is 3:1) and often reveal a multilocular appearance radiographically. Primary thymic MALT lymphomas are associated with autoimmune diseases, such as SjS, systemic lupus erythematosus (SLE), rheumatoid arthritis, and a monoclonal gammopathy of IgA rather than IgM/IgG. Complete surgical excision results in a good prognosis.

In conclusion, thymic MALT lymphoma is an important differential diagnosis of thymic neoplasms. In patients with anterior mediastinal multilocular cystic mass associated with immunological abnormalities, the possibility of primary thymic MALT lymphoma has to be considered as differential diagnosis, especially in cases of patients with SjS and also subclinical SjS.

5.5.6 Case 6

A 14-year-old man complained of intermittent fever for 20 days.

Chest CT: Multiple lymphadenopathy on the hilum, mediastinum, neck, and supraclavicular areas (Fig. 5.20).

[Diagnosis] Anaplastic large-cell lymphoma

[Diagnosis basis]The patient underwent a biopsy of the right supraclavicular lymph node, and the pathology showed anaplastic large-cell lymphoma (Fig. 5.21). Immunohistochemistry demonstrated positivity for ALK (Fig. 5.22), CD30 (Fig. 5.23), TIA, CD3, CD20, CD21, CD43, CD5, CD7, CD8, Mum-1, Pax-5, CD4 and CD163, and negativity for Bcl-2, CD10, and EBV.

[Analysis] Anaplastic large-cell lymphoma (ALCL) was first described in 1985 by Stein et al. and is a clinically, morphologically, and immunophenotypically heterogeneous neoplasm characterized by anaplastic large-cell kinase (ALK) expression, rearrangement of the ALK gene, and most characteristically its occurrence in children. According to the revised fourth edition of the WHO classification (2017), ALCL is defined as a CD30-positive tumor of T or null cell lineage, because these tumors are characterized by their anaplastic cytology and constant membrane expression of CD30 antigen.

There are two subsets of ALCL: Primary cutaneous ALCL that is confined to the skin, and Systemic ALCL that affects all organs (mainly the lymph nodes), with involvement of extranodal sites including skin, soft tissues, bone marrow,

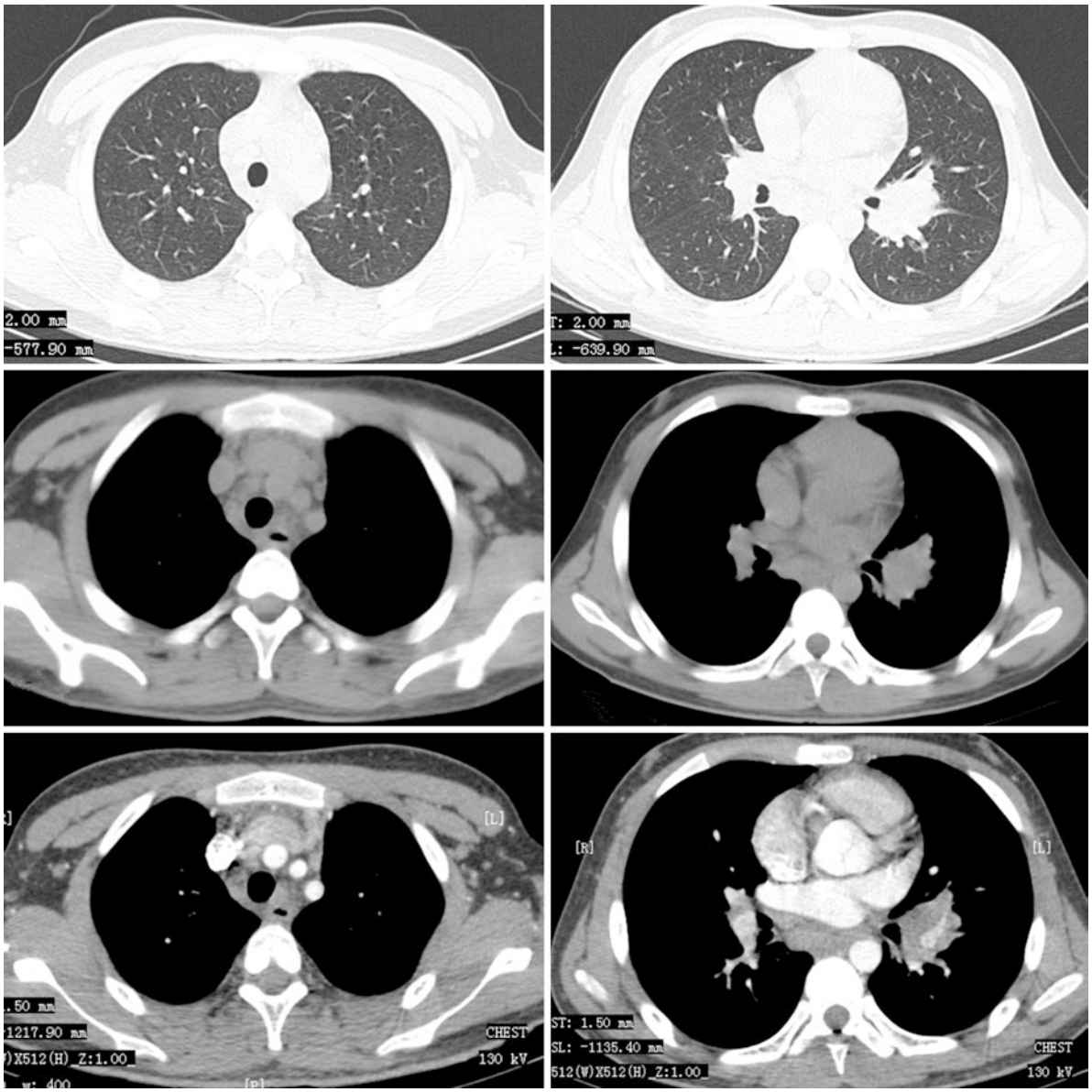

Fig. 5.20 Chest CT images of a 14-year-old man complained of intermittent fever for 20 days

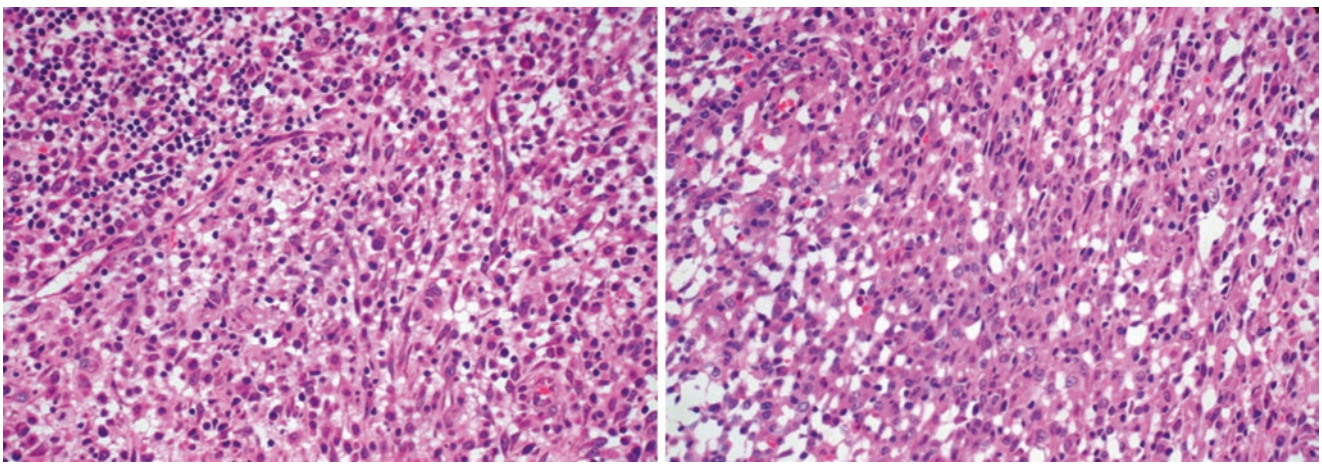

Fig. 5.21 Neoplastic cells are characterized by abundant cytoplasm and kidney-shaped nuclei with multiple abnormal mitotic figures

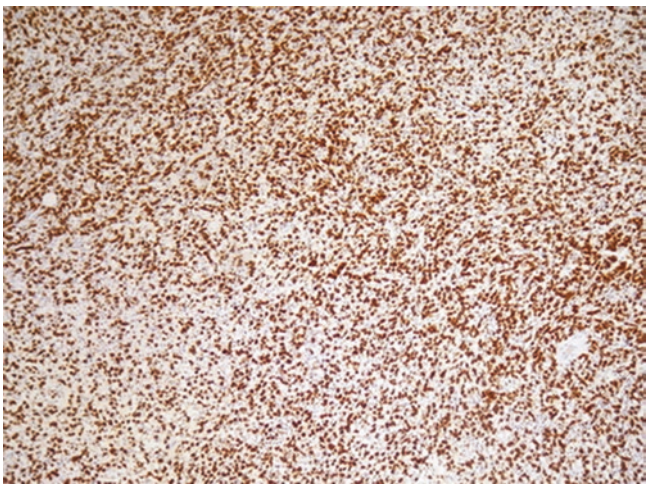

Fig. 5.22 Immunohistochemistry demonstrated strong positivity for ALK

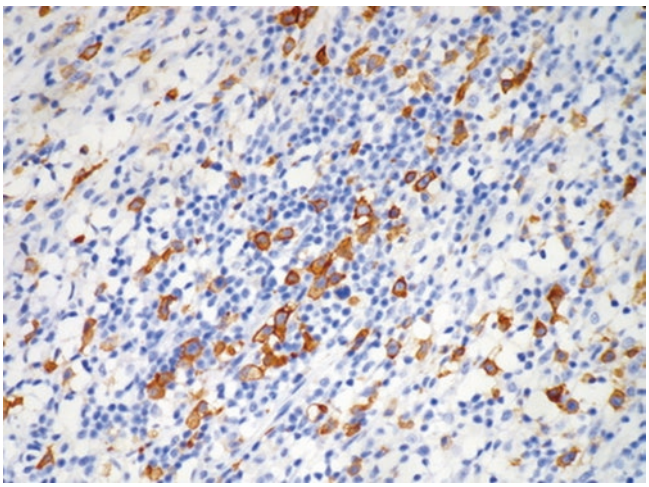

Fig. 5.23 Immunohistochemistry scattered positivity for CD30

lungs, and liver. The mediastinum is involved in about 10% (Fig. 5.24). Systemic ALCL is the most common type and mainly affects men. According to the expression of a protein called ALK, it can be divided into two main subtypes: ALK-positive ALCL accounts for 50–80% and is more common in young adults with a survival rate of 70–90% for 5 years, while ALK-negative ALCL represents 20–50% and tends to affect older adults with a worse prognosis and a survival rate of 40–60%.

Among hematologic malignancies, ALK rearrangements with nucleophosmin-1 (NPM1) and other partners are the most common and best characterized rearrangements. Most of the ALK-positive ALCLs have a t(2; 5) (p23;q35) fusing the ALK gene to NPM1; but these translocations may also occur with other partner genes, resulting in ALK fusion with TPM3, TPM4, TFG, ATIC, etc. The intracellular localization of the fusion protein is determined by these fusion partners. Various signaling pathways in ALK-positive ALCL cells were activated by the NPM-ALK fusion protein, including the JAK/STAT3, PI3K/AKT/mTOR, and has been shown to cause the accumulation of oncogenic CDC25A and myeloid cell leukemia-1 (MCL1) via a phosphorylation-dependent reaction. CDC25A belongs to the MPI phosphatase family. It is a tyrosine protein phosphatase that functions as a dosage-dependent inducer of mitotic progression. CDC25A is required for progression from G1 to the S phase of the cell cycle. MCL1 is a member of the B-cell lymphoma-2 (BCL-2) family known to play a significant role in the regulation of apoptosis. Other mechanisms via transcription factors such as the CCAAT/enhancer-binding protein beta (C/EBPβ) have also been shown to affect the survival and growth of ALK-positive ALCL neoplasms.

ALCL constitutes nearly 15% of pediatric NHL and 2% of all NHL. ALCL is classified as clinical stage III and characterized by B group symptoms typical of an aggressive lymphoma. Lymph node enlargement is more common than in other NHLs. Though it mostly involves lymph nodes, extranodal involvement is also seen in about 60% of the cases.

ALK-positive ALCL shows a broad morphologic spectrum. However, all cases contain a variable proportion of cells with eccentric, horseshoe- or kidney-shaped nuclei, which usually has an eosinophilic region near the nucleus. These cells are called as hallmark cells. Five morphologic patterns have been described in ALK-positive ALCL: a common pattern of large cells (60% of cases), lymphohistiocytic (10%), small cells (5–10%), Hodking-like (3%), or a combination of more than one of the above (15%). In general, ALCL tumor cells are positive for CD30 and EMA in most patients. About 60–85%of patients are also positive for ALK, and about 60% express one or more T cell-associated antigens such as CD43. Immunohistochemical staining of the trephine sections revealed a variable degree of CD3, CD4, and CD8 positivity. Cytotoxic antigens (granzyme B, TIA1, and perforin) are usually expressed. Because the detection of ALK demonstrates almost 100% correlation with the presence of a chromosomal translocation, immunohistochemistry has replaced molecular tests to diagnose ALK-positive ALCL. In most cases with the t(2; 5) translocation, ALK staining of neoplastic cells is both cytoplasmic and nuclear. A membranous or diffuse and granular cytoplasmic distribution may be shown in variant translocations. In this particular case, the presence of cytoplasmic and membranous granular staining for ALK suggests the variant translocation with the clathrin gene t(2p23; 17q23).

The prognosis of ALCL is superior to other T-cell lymphomas. CHOP regimen is still the most used initial therapy. As a monoclonal antibody that binds to CD30 and causes tumor cell apoptosis, Brentuximab vedotin (BV) is also used in

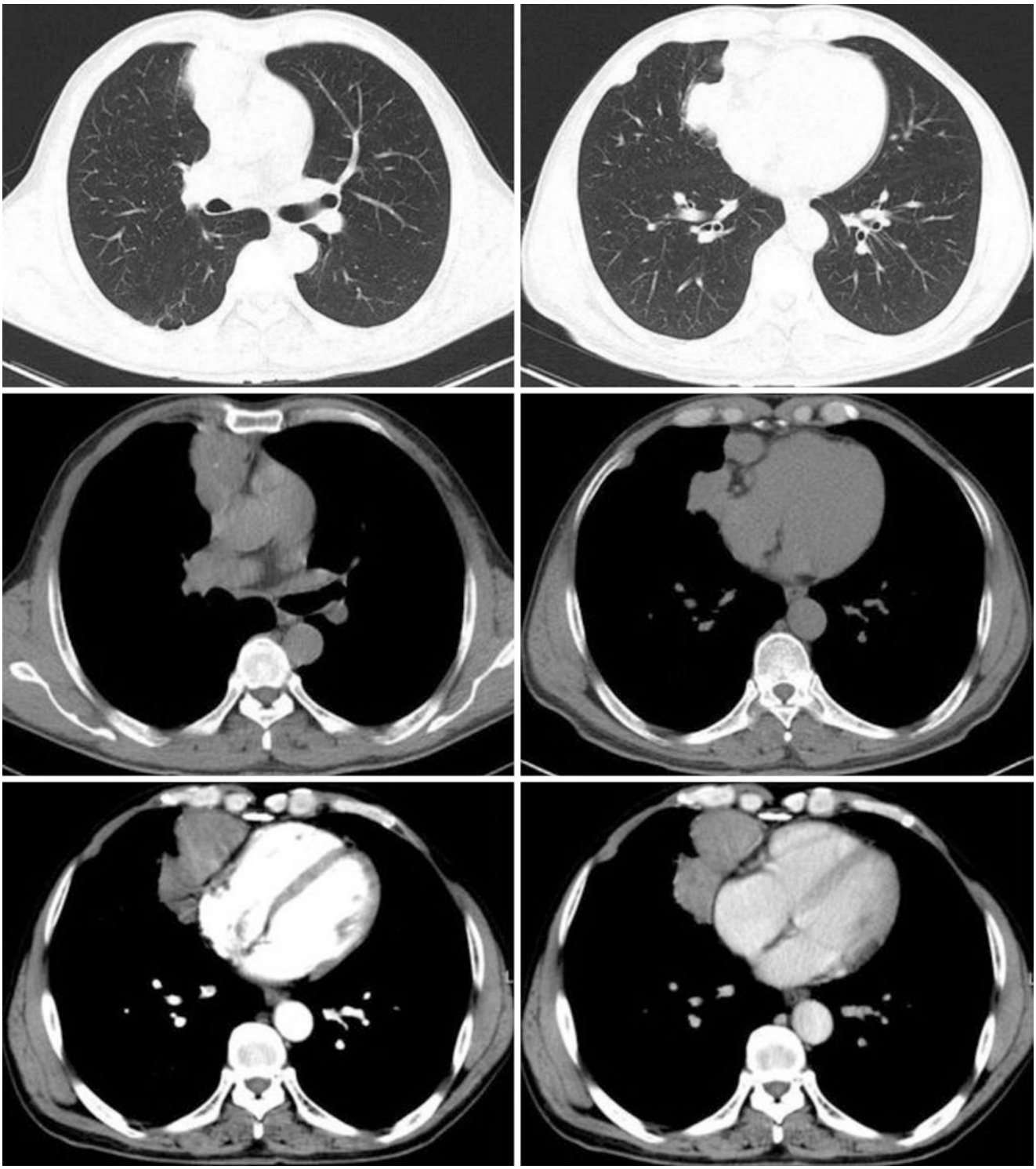

Fig. 5.24 A 50-year-old man with ALK-positive ALCL. Tumor infiltrated chest wall and lung tissue

refractory or relapsed ALCL, and has also been studied for allogenic transplant. Recent studies have shown that the median PFS in patients treated with BV was significantly longer than those of the most recent prior therapy in T cell lymphoma with CD30 expression. Mediastinum and (or) internal organ invasion are strong risk factors for poor outcome, as these patients have a high possibility of recurrence.

5.5.7 Case 7

A 16-year-old man complained of chest pain for 1 month and found a soft tissue mass in the anterior mediastinum for 1 week.

Chest CT: A right anterior mediastinum mass and a small amount of pleural effusion on the same side (Fig. 5.25).

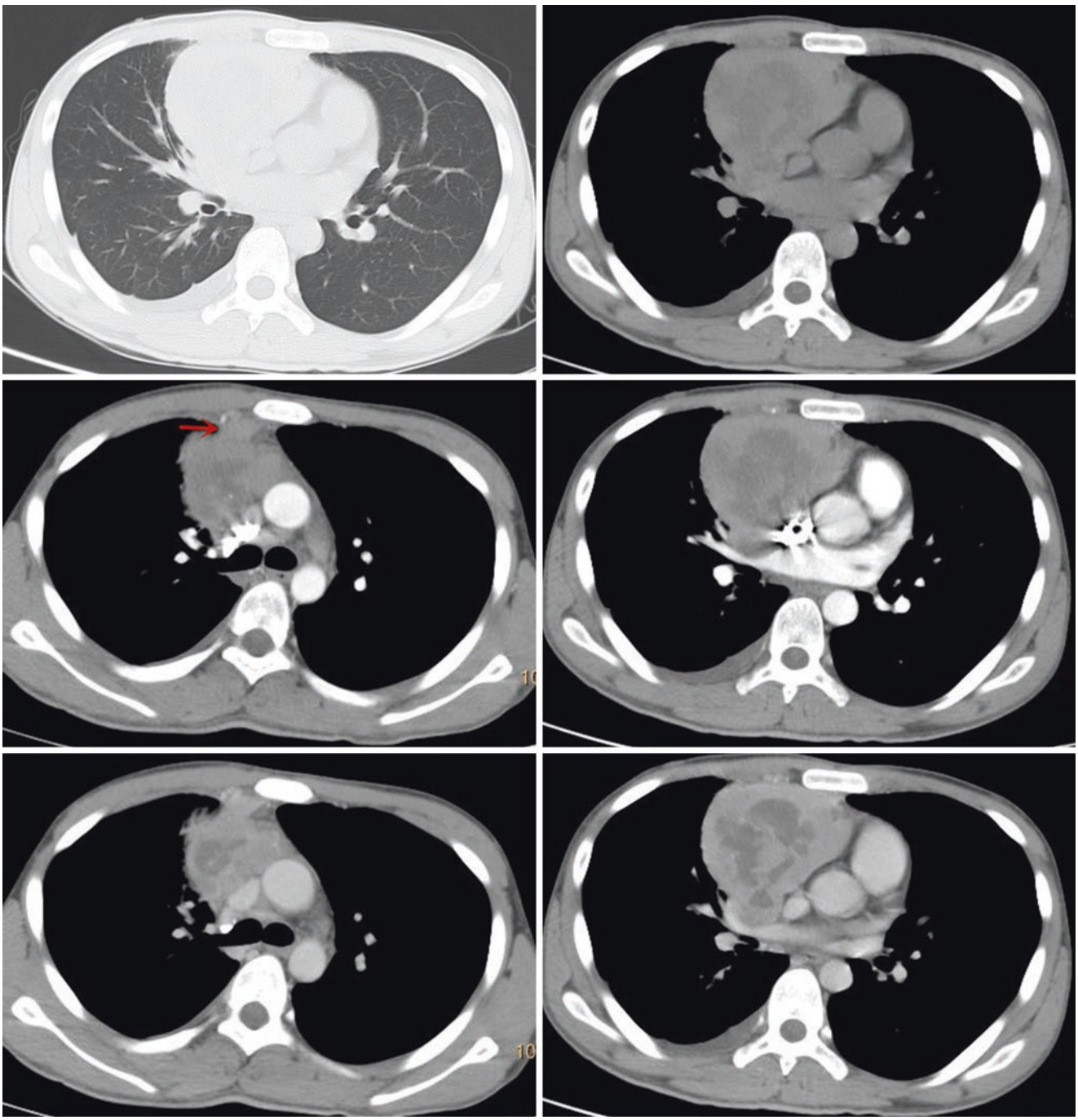

Fig. 5.25 Chest CT images of a 16-year-old man complained of chest pain for 1 month

[Diagnosis] Mediastinal T-lymphoblastic lymphoma

[Diagnosis basis] The right anterior mediastinal lesion involved the superior vena cava and pericardium, and the lymph node in the right internal mammary area was enlarged (red arrows), the above features are consistent with the diagnosis of lymphoma. The patient's mediastinal tumor biopsy showed the diagnosis of thymoma, and surgery was selected. Intraoperatively, the tumor measured 10 cm × 8 cm × 6 cm located in the anterior superior mediastinum region, invading the right upper lobe, superior vena cava, and pericardium. Pathological diagnosis was a T-lymphoblastic lymphoma, invading lung tissue, and hilar lymph node (1/1). Immunohistochemistry demonstrated positivity forCD3, CD5, CD43, CD1a, TdT, CD7, and CD10, and negativity forCD20, CD79a, CD30, CD15, CD34, CyclinD1, MPO, SALL-4, Ckpan, and CK19.The staining index for Ki-67 was about 90%. PET-CT showed that mediastinal lymphoma recurred after 1 month and involved lymph nodes (Fig. 5.26).

[Analysis] Lymphoblastic lymphoma (LBL) is a neoplasm of immature B cells committed to the B-(B-LBL) or T-cell lineage (T-LBL) that accounts for approximately 2% of all lymphomas. LBL is the second most common type of NHL in childhood and adolescence, accounting for 25–35% of all cases. The vast majority is of T-lymphoblastic origin (T-LBL, 70–80%) with only 20–25% arising from B lymphoblasts (B-LBL) and mixed myeloid/lymphoblastic (MPAL) phenotypes being very rare. A bone marrow involvement <25% (or 20% according to WHO) formally distinguishes LBL from acute lymphoblastic leukemia (ALL). Despite several genetic similarities, T-LBL and T-ALL demonstrate differences in BCL-2 expression and AKT signaling, resulting in differences in clinical presentation.

As in other NHLs, the vast majority of LBLs are considered to be idiopathic, although some cases may be caused by autoimmune or inflammatory conditions or exposure to radiation or chemicals. T-cell receptor cytogenetic abnormalities and clonal rearrangements are frequently found in T-LBL and may participate in its pathogenesis by driving altered expression of T-cell oncogenes. In T-LBL cytogenetic abnormalities involving the 14q11–13 region (T-cell receptor alpha/delta genes) are frequent (50–70%), and include inv. (14)(q11; q32), and chromosomes 9, 10, and11. Rearrangements of T-cell receptor beta (TRB; 7q34) and T-cell receptor gamma (TRG; 7p14.1) genes are also common.

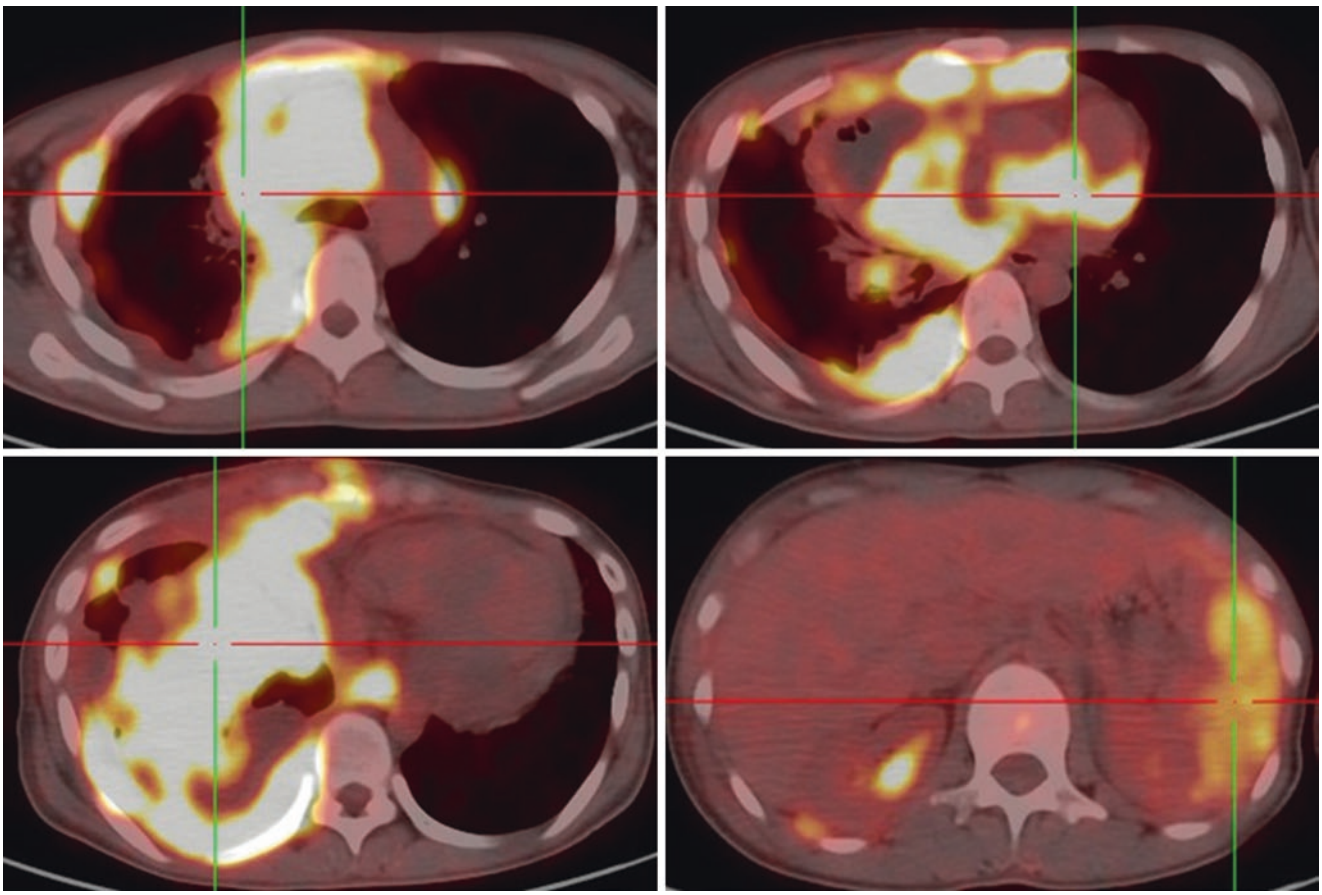

Fig. 5.26 Mediastinal lymphoma relapses after surgery with extensive metastases

Histologically, T-LBL shows an infiltrate of small, round blue cells. The diagnosis needs to be further confirmed by flow cytometry of malignant effusions and/or fresh tissue or immunohistochemical analysis of paraffin-embedded biopsies. T-LBLs express cytoplasmic or membrane-bound CD3, which is specific for the T lineage. In addition, most terminal deoxynucleotidyl transferases (TdT) were positive, while CD1a, CD2, CD4, CD5, CD7, and CD8 were variably positive. They are further subdivided by the differentiation stage of T lymphoblasts on their passage through the thymus. TdT expression has been identified as the best marker for determining the precursor cell nature of a lymphoma. In addition to TdT, the most specific markers to indicate the precursor nature of T lymphoblasts are CD99, CD34, and CD1a. In TdT-negative lymphoma with typical lymphoblastic morphology, either expression of CD1a or CD34, coexpression of CD4 and CD8, or coexpression of CD79a and CD3 can be used to determine the precursor cell nature of lymphoma.

T-LBL affects males 2.5 times more often than females and the median age of T-LBL diagnosis is around 9 years of age. T-LBL can arise in any lymph node of the body but the mediastinal, cervical, supraclavicular, and axillary nodes are involved in the vast majority of patients (Fig. 5.27). The mediastinal mass is anterior, bulky, and associated with pleural effusions, superior vena cava syndrome, tracheal obstruction, and pericardial effusions (Fig. 5.28). Necrosis within the mass is more common (Fig. 5.29). Symptoms include cough, shortness of breath, stridor, dyspnea, and acute respiratory distress. Edema of the neck and face and jugular venous distension should cause the suspicion of superior vena cava syndrome. They show stage IV disease (80%) and B symptoms (50%), and elevated serum lactate dehydrogenase (LDH) levels in the majority of cases. Less commonly, patients present extranodal disease (e.g., skin, testis, and bone involvement). Abdominal dissemination is unusual, but if it exists, it mainly affects the liver and spleen. About 15–20% of patients exhibit bone marrow infiltration. At presentation, 5−10% of cases has central nervous system involvement.

Standard therapeutic option for patients with LBL is based on intensive multidrug leukemia chemotherapy regimens. These regimens contain 7–10 drugs, such as cyclophosphamide, methotrexate, prednisone, vincristine, cytarabine, thioguanine, l-asparaginase, nitrosoureas, etopo-

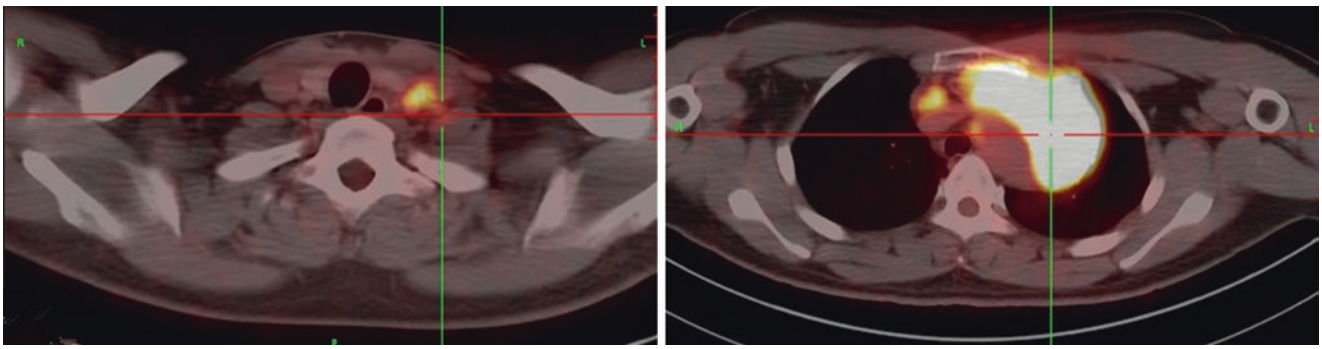

Fig. 5.27 A 31-year-old man had T-LBL with involvement of the mediastinum and left supraclavicular lymph nodes

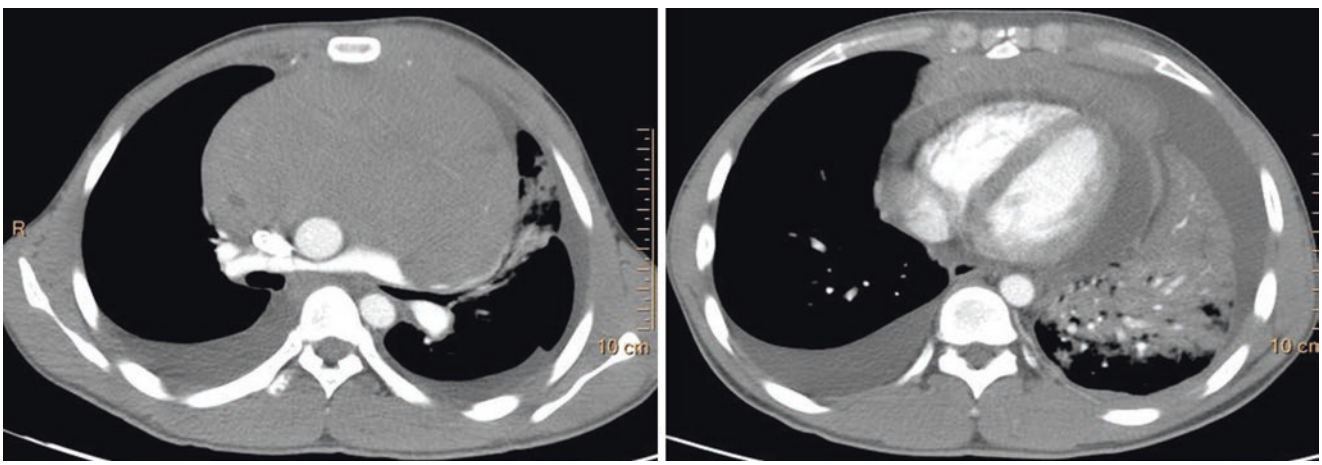

Fig. 5.28 A 23-year-old man had T-LBL in the anterior mediastinum with pericardial and pleural effusions

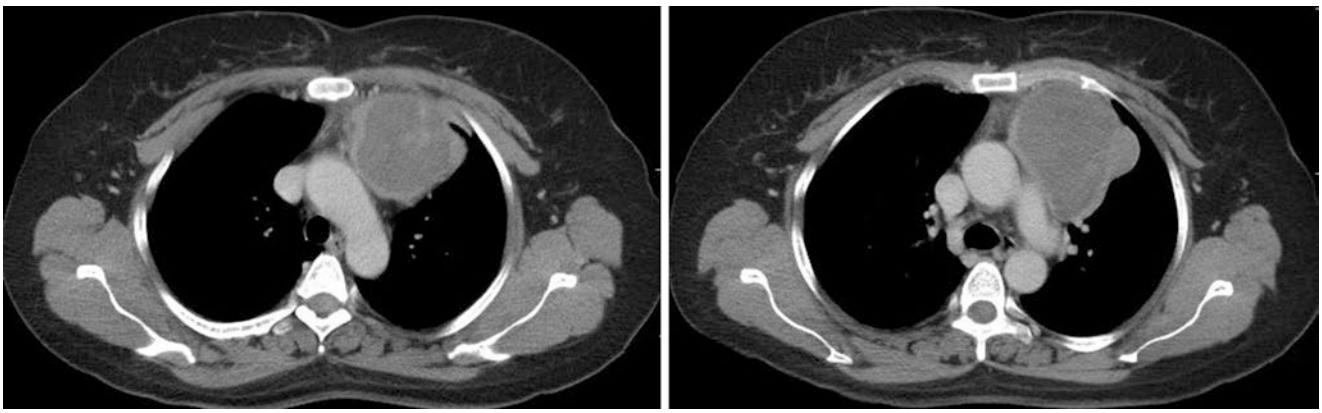

Fig. 5.29 A 36-year-old woman had T-LBL in the left anterior mediastinum with obvious necrosis and clear boundary

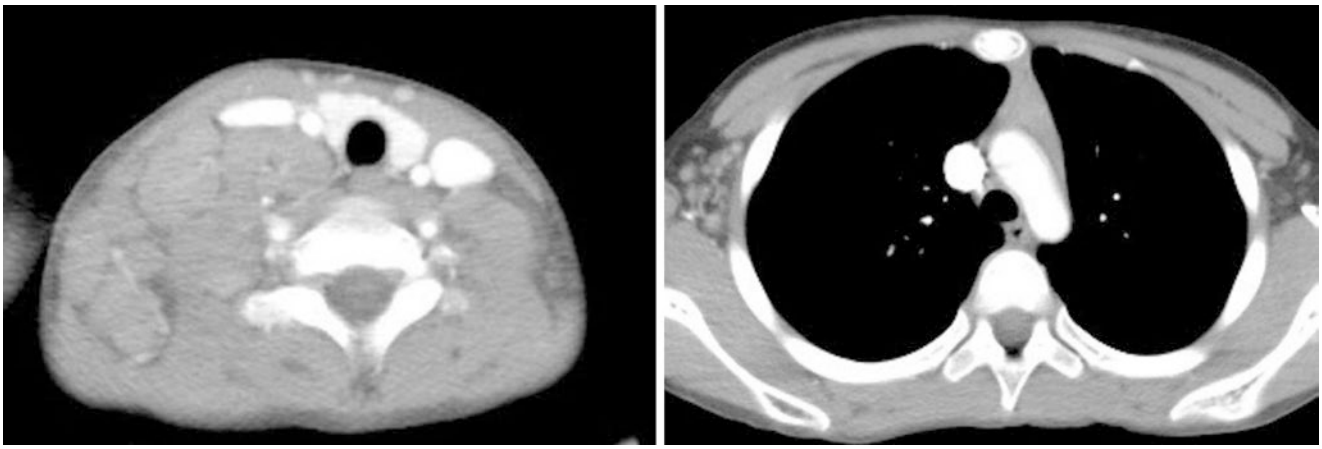

Fig. 5.30 Multiple lymphadenopathy in the right neck, supraclavicular area, and axilla

side, and anthracyclines, including intensive intrathecal chemotherapy. For patients with limited or advanced disease, the chemotherapy regimens do not substantially change. Therapeutic approaches to LBL included conventional regimens for NHL, intensive chemotherapy protocols designed for high-grade NHL and protocols for the treatment of ALL, whether or not prophylactic cranial irradiation and prophylactic or therapeutic mediastinal irradiation. The change from NHL protocols to ALL-based protocols has greatly improved CR rates and survival rates in adults with T-LBL. Certain pediatric NHL protocols improved survival in childhood LBL (e.g., LSA2-L2 and LNH-84), while this was not the case in adult disease. Nevertheless, these early studies have demonstrated that LBL patient survival was increased by prolonged, intensified chemotherapy and CNS prophylaxis. Furthermore, SCT, mostly autologous SCT (ASCT) was included to different extent in treatment strategies.

Treatment options at relapse include aggressive chemotherapy-based regimens and SCT, but the effect is poor. For example, the OS at 5 years after relapse was 14% in a retrospective analysis of children and adolescents with relapsed T-LBL. Only a few patients who can undergo allogeneic SCT can achieve long-term survival. T cell-targeting immunotherapy or new cytostatic drugs (such as nelarabine) may be more effective than existing interventions for treating relapse in T-LBL patients, but they still need to be evaluated in prospective trials.

Despite the significant advances achieved in LBL therapy, several issues such as the management of CNS and mediastinal disease and the role of SCT remain a matter of debate and research.

5.5.8 Case 8

An 11-year-old boy found multiple enlarged lymph nodes in his right neck. Chest CT showed multiple lymphadenopathy in the right neck, supraclavicular area, and axilla (Fig. 5.30). The biopsy pathology showed classic Hodgkin's lymphoma, with lymphocytes predominantly. After 2 cycles of chemotherapy, PET-CT examination showed no obvious abnormal

metabolism, and the therapeutic effect was evaluated as complete remission. Continuing chemotherapy for 2 cycles, chest CT showed no enlarged lymph nodes in the neck, supraclavicular area, and axilla, and anterior mediastinal thymus hyperplasia (Fig. 5.31). Half a year later, CT scan showed that the thymus had further hyperplasia (Fig. 5.32).

[Diagnosis] Rebound thymic hyperplasia

[Analysis] Rebound thymic hyperplasia (RTH) is defined as an increase in thymus size relative to previous CT scans when patients achieved complete remission after chemotherapy. The development of thymic enlargement is not only present in patients with lymphoma after chemotherapy, but also in patients with other malignant tumors or conditions. RTH has been reported in patients with osteosarcoma, germ cell tumor, nasopharyngeal carcinoma, synovial sarcoma, breast cancer, lung cancer, colon cancer, and Wilms' tumor after chemotherapy. RTH was found by Kissin et al. [3] in 11.6% of their patients with testicular teratomas after chemotherapy. The incidence of RTH as 1.49% after radioactive iodine ablation therapy was reported by Jeon et al. in patients with thyroid cancer. RTH has also been described after recovery from stress such as pneumonia, operation, after administration of steroids, and bone marrow transplantation.

Some authors believe that RTH developing after chemotherapy indicates a good prognosis. Thymic hyperplasia could represent the recovery of the host immune system, especially cell-mediated immunity, an immunologic rebounding phenomenon, and it could reflect stronger immune surveillance for children with lymphoma and is conducive to successful control of lymphoma. RTH mostly happens within the first year following chemotherapy. It is usually observed in children but may also occur in young adults.

RTH developed in 67.7% of pediatric patients with lymphoma achieving complete remission after chemotherapy.

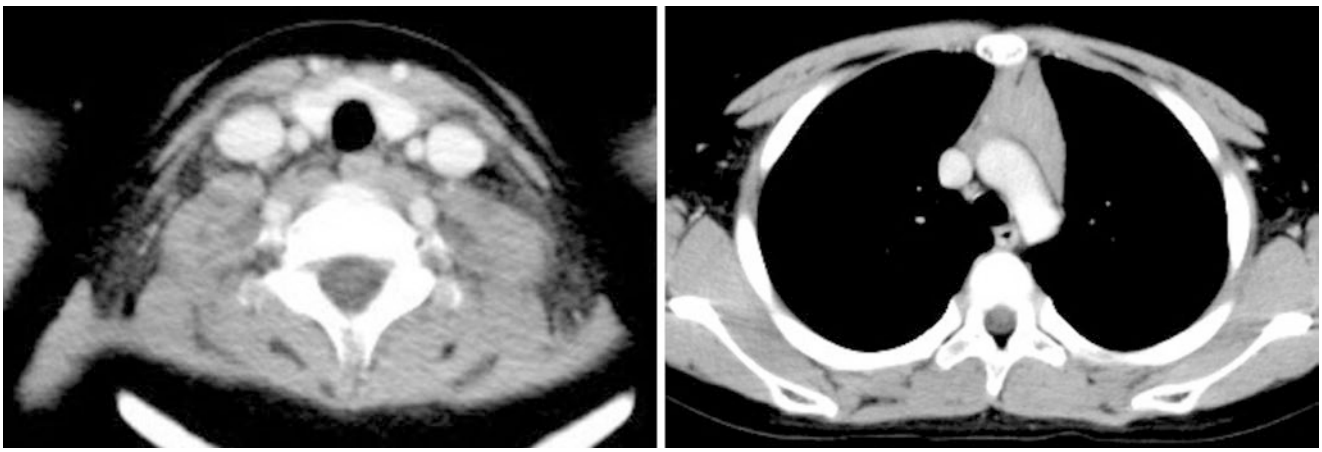

Fig. 5.31 Chest CT showed thymic hyperplasia

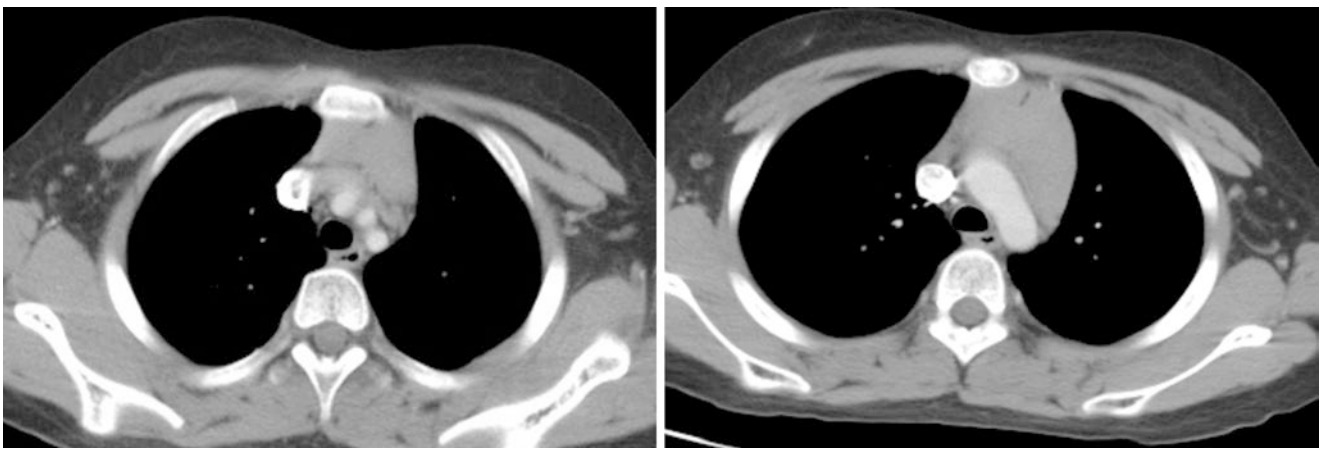

Fig. 5.32 The thymus was further enlarged

Differentiation of RTH from lymphoma relapse is essential for clinicians. Some reports attempted to distinguish RTH from lymphoma relapse through chest CT morphology. Yarom et al. [6] suggested that features, such as arrowhead-shaped triangular structure and bilobulated configuration with convex borders, being located in the normal site of the thymus, and homogeneous soft tissue density, favored RTH.PET-CT is a modality for lymphoma staging and follow-up, but it is not able to distinguish RTH from thymic tumors. Thymus shows physiological FDG uptake in prepubertal age and sometimes in young adults. MRI is a helpful problem-solving tool for evaluation of the thymus. It is superior to CT in distinguishing cystic from solid lesions and hyperplastic thymus from thymic tumors. Chemical-shift MRI, which includes signal-intensity index and chemical-shift ratio, has high accuracy in distinguishing thymic hyperplasia from tumors.

In summary, if there is only thymic enlargement without other lymphadenopathy at follow up, RTH may be considered. Otherwise, RTH will be misclassified as thymic relapse according to the revised response criteria.

References

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