Pediatr Radiol (2018) 48:279–282
DOI 10.1007/s00247-017-3961-3

CASE REPORT

Imaging findings of Copa syndrome in a 12-year-old boy

Razan Noorelahi[1] · **Geovany Perez**[2] · **Hansel J. Otero**[1]

Received: 2 December 2016 / Revised: 25 May 2017 / Accepted: 3 August 2017 / Published online: 28 September 2017

Abstract Copa syndrome is a newly described autosomal dominant autoinflammatory disease that presents as pulmonary hemosiderosis and polyarticular arthritis. Twenty-one cases from five families have been reported to date. We present chest computed tomography (CT) and temporomandibular joint magnetic resonance (MR) findings of a 12-year-old boy presenting with dyspnea on exertion, fatigue and clubbing. Additional findings included a restrictive pattern of pulmonary involvement and positive inflammatory markers and autoantibodies. Genetic testing revealed a p.W240R variant of the COPA gene confirming the diagnosis of Copa syndrome. CT of the chest showed a nonspecific interstitial pneumonia pattern distributed mainly in the lower lobes. MR of the temporomandibular joints and follow-up CT three years later are also described.

Keywords Autosomal dominant missense mutation · Child · Computed tomography · Copa syndrome · Nonspecific interstitial pneumonia · Pulmonary hemosiderosis · Temporomandibular joint arthritis

✉ Razan Noorelahi
noorelahi.razan@gmail.com

[1] Department of Diagnostic Imaging and Radiology, Children's National Health System, The George Washington University School of Medicine & Health Services, 111 Michigan Ave. NW, Washington, DC 20010, USA

[2] Pulmonary & Sleep Medicine Division, The George Washington University School of Medicine & Health Sciences, Washington, DC, USA

Introduction

Copa syndrome is an autosomal dominant multisystem autoinflammatory disease that affects the lungs, joints and kidneys. It was first included in the 2015 update of the Primary Immunodeficiency Disease classification by the International Union of Immunological Societies' Expert Committee for Primary Immunodeficiency. It is listed as a non-inflammasome disorder. Other conditions in this category include pyogenic sterile arthritis, pyoderma gangrenosum, acne (acronymed PAPA) syndrome, Blau syndrome, ADAM17 (Disintegrin and Metalloproteinase Domain 17) deletion, chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome), DIRA (Deficiency of the Interleukin 1 Receptor Antagonist), DITRA – Deficiency of the IL-36 receptor antagonist, SLC29A3 (Solute Carrier Family 29 Member 3) mutation, CAMPS (Caspase recruitment domain-containing protein 14), which is a CARD14 mediated psoriasis, cherubism, and CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy) [1].

Copa syndrome is inherited in an autosomal dominant pattern and is a multisystemic immune dysregulation affecting lungs, joints and kidneys. Pulmonary involvement is usually in the form of pulmonary hemorrhage presenting with tachypnea, cough and hemoptysis. The most frequent joint presentation is nonerosive polyarticular arthritis affecting the knees and interphalangeal joints. Renal involvement has a wide array of pathological and clinical manifestations [2, 3].

Twenty-one cases have been reported in the medical literature [2, 3]. Previous publications have shown the pulmonary findings as seen on computed tomography (CT) [2, 4]. Here, we report a case of genetically confirmed Copa syndrome with chest CT findings resembling nonspecific interstitial pneumonia progressing from predominantly ground glass opacities to

Table 1 Pulmonary function testing at presentation with the predicted values for a matched patient

	Actual	% predicted
TLC (L)	2.01	75
RV (L)	1.31	204
RV/TLC	65	
DLCO (ml/min/mmHg)	3.69	24
DLCOcor (ml/min/mmHg)	3.82	25
DLCO/VA (ml/min/mmHg/L)	4.19	73

DLCO carbon monoxide diffusing capacity, *DLCOcor* DLCO corrected to hemoglobin, *RV* residual volume, *TLC* total lung capacity, *VA* alveolar volume

a more diffuse reticular pattern with cyst formation at the 3-year follow-up.

Case report

A 12-year-old African-American boy presented to the pulmonary clinic for a second opinion regarding the need for pulmonary biopsy after a course of immunosuppressants for suspected idiopathic pulmonary hemosiderosis. Initial presentation included a history of exercise intolerance and failure to thrive with recurrent episodes of nonproductive cough and respiratory distress without hemoptysis. Physical examination showed height and weight at the 1st percentile and below the 1st percentile, respectively, as well as finger clubbing. Pulmonary function test showed a severe restrictive lung defect with total lung capacity (TLC): 25% of predicted; air trapping with residual volume/total lung volume (RV/TLC): 65; decreased diffusing capacity of carbon monoxide (DLCO): 25% of predicted, and diffusing capacity of carbon monoxide/alveolar volume (DLCO/VA): 73% of predicted (Table 1). Bronchoalveolar lavage pathological examination showed mixed cell population, predominantly alveolar macrophages, mild to moderate increase in lipid-laden macrophages and numerous hemosiderin-laden macrophages. CT of the chest showed interstitial lung disease closely resembling nonspecific interstitial pneumonia including ground glass opacities, septal thickening and cyst formation (Fig. 1).

Several months later, he presented with morning stiffness and polyarticular pain including right temporomandibular joint pain with decreased mouth aperture. MRI confirmed inflammatory changes without erosions (Fig. 2) while radiographic evaluation of other involved joints, such as the knees, was normal (not shown).

Laboratory tests results (Table 2) showed positive HLA-B27, high erythrocyte sedimentation rate, C-reactive protein, C3 complement, rheumatoid factor, antinuclear antibody (ANA) titer of 1:80 with a homogenous pattern, and a strong positive anti-cyclic citrullinated peptide. However, he was negative for tissue transglutaminase antibodies, anti endomysial Ab IgA, centromere antibodies, myeloperoxidase antibodies, antineutrophil cytoplasmic antibodies, anti-ENA (extractable nuclear antigen), ENA1a, SCL-70, and a normal level of C-reactive protein.

Genetic testing identified a missense mutation, p.W240R, in the COPA gene, which confirmed Copa syndrome. Follow-up CT 33 months after the initial diagnosis (at age 14) showed interval decrease of ground glass opacities, which were partially replaced by a reticular pattern of interstitial thickening and cyst formation (Fig. 3)

Since the last imaging follow-up at 33 months after initial presentation, the patient has been maintained on methotrexate, adalimumab and naproxen for 24 months with no active pulmonary or arthritic complaints

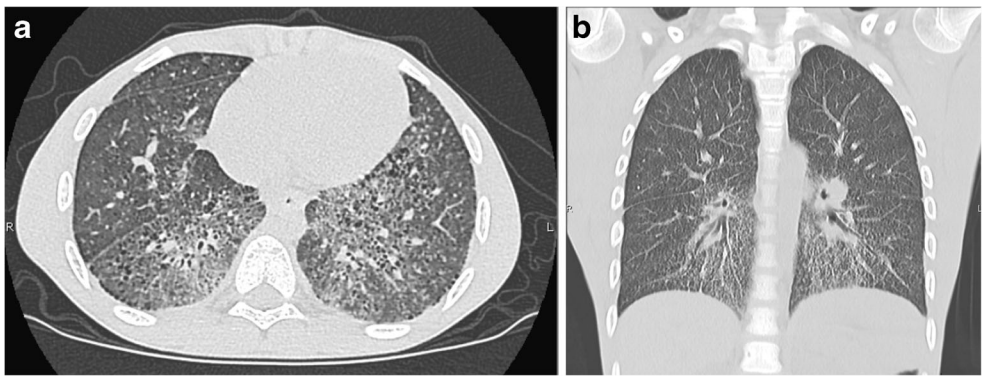

Fig. 1 Initial CT of the chest. Axial CT image (**a**) in lung window shows bilateral ground glass opacities in a reticular pattern with cyst formation and septal and bronchial wall thickening in a bronchovascular and subpleural distribution. Coronal CT image (**b**) demonstrates the basal distribution of the disease with mild ground glass opacities. The overall pattern in this patient is consistent with nonspecific interstitial pneumonia. Please note that typical findings of alveolar hemorrhage including extensive ground glass and interlobular septal thickening (typically referred to as crazy paving) are lacking

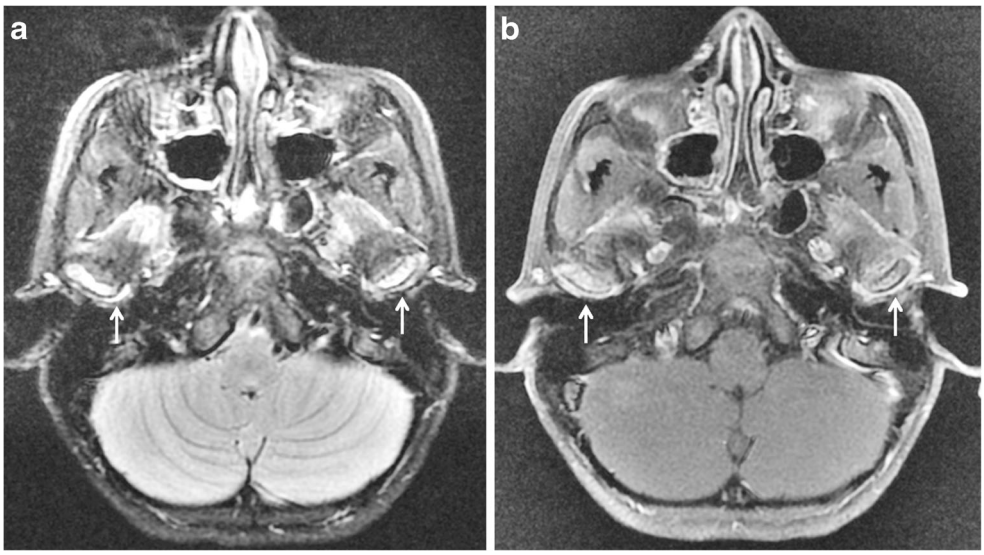

Fig. 2 MRI of the temporomandibular joint. Axial T2-weighted MRI (**a**) with fat saturation (TE: 72; TR: 3,600) and (**b**) axial contrast-enhanced T1-weighted MRI with fat saturation (TE: 11; TR: 600) show bilateral edema of the mandibular heads and associated synovial thickening and enhancement (*arrows*). No bone erosions or early degenerative changes were seen

Discussion

Copa syndrome is a newly described disease in the pediatric literature with only 21 reported cases, all arising from five families [2]. The mutant COPA gene results in increased endoplasmic reticulum stress due to impaired anterograde and retrograde intracellular trafficking from the endoplasmic reticulum to Golgi and vice versa [4, 5].

Table 2 Laboratory study values on several follow-up occasions

Test (unit)	Patient result	Normal range
ESR (mm/Hr)	79	0-20
CRP (mg/dl)	1.71	0.08-0.76
RF (IU/ml)	72	<14
Anti-CCP (U)	250	<25
Automated monocytes (%)	13.5	4.4-12.3
Automated lymphocytes (%)	44.9	6.5-32.9
CD3 (%)	47	63-79
CD3+CD4+ (%)	35	41-56
CD3+CD8 (%)	10	21-31
Natural killer cells (%)	18	5-15
B cell (%)	32	6-15
C3 compliment (mg/dl)	132	75-107
C4 compliment (mg/dl)	16.3	21-38
IgG (mg/dl)	2.628	685–1,620
IgA (mg/dl)	323	46-218
IgM (mg/dl)	99	27-151

Anti-CCP anti-cyclic citrullinated peptide, *CRP* C-reactive protein, *CD* cluster of differentiation *ESR* erythrocyte sedimentation rate, *Ig* immunoglobulin, *RF* rheumatoid factor

We report a case of genetically confirmed Copa syndrome with pulmonary and rheumatological manifestations. Previous description of pulmonary involvement includes alveolar hemorrhage with subsequent pulmonary fibrosis, which in CT presents as diffuse ground glass opacities with septal thickening and cyst formation [2]. In our case, the CT findings are somewhat similar with ground glass opacities in a reticular pattern with cyst formation, and septal and bronchial wall thickening in a bronchovascular and subpleural distribution. These descriptors are typically associated with nonspecific interstitial pneumonia. Nonspecific interstitial pneumonia, however, typically affects patients in the 40- to 50-year-old age group and is most commonly idiopathic in that adult population [6]. Pediatric nonspecific interstitial pneumonia was previously described to manifest in different pathologies including congenital surfactant dysfunction and autoimmune diseases [7].

Although many cases of nonspecific interstitial pneumonia are idiopathic, it can be seen in association with a number of drugs, connective tissue disease and hypersensitivity pneumonitis [8]. As demonstrated above, nonspecific interstitial pneumonia can also be associated with the newly described Copa syndrome. The presence of predominant ground glass and reticular opacities is highly characteristic of nonspecific interstitial pneumonia. Common additional CT findings include confluent areas of ground glass attenuation, often with lower or peribronchiolar predominance. Nonspecific interstitial pneumonia is thought to represent varying degrees of interstitial inflammation and fibrosis that are temporally and morphologically homogeneous. The areas of ground glass opacities correspond histologically to alveolar

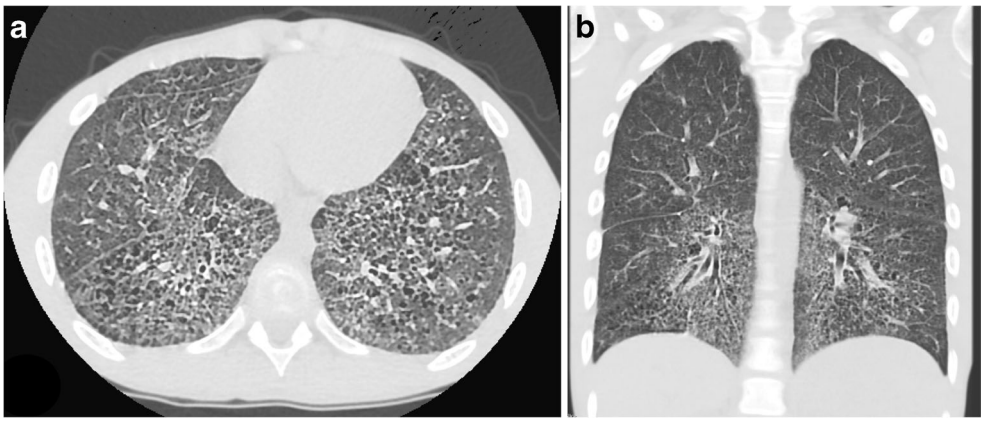

Fig. 3 Follow-up CT of the lungs after 33 months after initial diagnosis in a now 14-year-old boy with Copa syndrome. Axial CT image (**a**) in lung window shows progression of reticularity and bilateral cyst formation, with increased septal and bronchial wall thickening as well as bronchiolectasis. Coronal CT image (**b**) demonstrates persistent predominantly basal distribution now involving the upper lobes and with minimal residual ground glass opacities

septal thickening by inflammatory cells and fibrous tissue. The airspace opacities of acute lung injury are absent [8].

Our patient had complaints of arthralgia in his shoulders, knees and feet. Several radiographs were obtained and showed mild generalized osteopenia. Bilateral temporomandibular joint involvement was also clinically present. Our patient was placed on different courses of immunosuppressants such as etanercept and subsequently showed improvement in terms of subsided arthralgias and improved respiratory symptoms when on adalimumab and methotrexate. Additional pulmonary medications including montelukast and albuterol were prescribed to be taken as needed.

This case report highlights the pulmonary CT findings of Copa syndrome, presenting as a nonspecific interstitial pneumonia. Future research should include a multi-institutional registry of this rare newly described disease in order to build a case series from which more substantial conclusions can be drawn.

Compliance with ethical standards

Conflicts of interest None

References

1. Picard C, Al-Herz W, Bousfiha A et al (2015) Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for primary immunodeficiency 2015. J Clin Immunol 35:696–726
2. Vece TJ, Watkin LB, Nicholas SK et al (2016) Copa syndrome: a novel autosomal dominant immune dysregulatory disease. J Clin Immunol 36:377–387
3. de Jesus AA, Goldbach-Mansky R (2015) Newly recognized Mendelian disorders with rheumatic manifestations. Curr Opin Rheumatol 27:511–519
4. Watkin LB, Jessen B, Wiszniewski W et al (2015) COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. Nat Genet 47:654–660
5. Popoff V, Adolf F, Brügger B et al (2011) COPI budding within the Golgi stack. Cold Spring Harb Perspect Biol 3:a005231
6. Kligerman SJ, Groshong S, Brown KK et al (2009) Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations. Radiographics 29:73–87
7. Das S, Langston C, Fan LL (2011) Interstitial lung disease in children. Curr Opin Pediatr 23:325–331
8. Ferguson EC, Berkowitz EA (2012) Lung CT: part 2, the interstitial pneumonias–clinical, histologic, and CT manifestations. AJR Am J Roentgenol 199:W464–W476