The Turkish Journal of Pediatrics 2022; 64: 394-399
https://doi.org/10.24953/turkjped.2020.2997

Case Report

A case of juvenile systemic sclerosis and congenital pulmonary airway malformation related mucinous adenocarcinoma of the lung: paraneoplastic syndrome or just a coincidence?

Ayten Aliyeva[1], Amra Adrovic[1], Süheyla Ocak[2], Şebnem Batur[3], Mehmet Yıldız[1], Fatih Haşlak[1], Oya Köker[1], Sezgin Şahin[1], Kenan Barut[1], Özgür Kasapçopur[1]

Departments of [1]Pediatric Rheumatology, [2]Pediatric Hematology and Oncology and [3]Pathology, İstanbul Cerrahpaşa University Faculty of Medicine, İstanbul, Turkey.

ABSTRACT

Background. Juvenile systemic sclerosis (JSS) is an extremely rarely seen auto-immune disease characterized by the increased fibrosis of skin and internal organs. Congenital pulmonary airway malformation (CPAM) is a developmental disorder of the lung, characterized by atypical cell hyperplasia which creates the ground for lung adenocarcinoma. In general, CPAM is diagnosed in early childhood, due to recurrent respiratory symptoms including cough, hemoptysis and respiratory infections. Although rare, there are some sporadic asymptomatic cases of CPAM that have been reported. We present a case with a coincidental presence of two rare diseases: JSS and CPAM.

Case. An adolescent female patient was admitted to hospital due to clinical signs of JSS. During the follow-up, the patient had been diagnosed with cystic adenoid malformation of the lung complicated by mucinous adenocarcinoma. The patient was previously healthy with an unremarkable history, including lack of respiratory symptoms. Left inferior lobectomy was performed. Considering the small size of malignant loci, the total resection of the tumor and absence of any sign for metastasis disease, adjuvant therapy was not scheduled.

We haven't found a pediatric case of CPAM associated adenocarcinoma of the lung presented by signs of JSS in the literature. In this case, the clinical signs of JSS possibly represent part of the paraneoplastic syndrome related to adenocarcinoma of the lung.

Conclusions. Internal organ involvement, including respiratory system, should not be omitted even in asymptomatic patients with JSS. Auto-antibody negativity represents a clue for the possible underlying condition. Further studies with a higher number of patients would reveal more relevant data.

Key words: adenocarcinoma, congenital pulmonary airway malformation, juvenile systemic sclerosis, KRAS.

Juvenile systemic sclerosis (JSS) is an extremely rare multisystemic disease characterized by skin stiffness, vasculopathy and internal organ involvement.[1-4] The precise worldwide incidence of the disease is unknown. The disease pathophysiology is not completely explained. Possible triggers (infections, trauma, chemicals etc.) initiate an auto-immune response which is characterized by the production of auto-antibodies and increased skin and internal organ fibrosis.[1,3]

Studies among adults reported an increased frequency of malignancies (namely lung cancer) in patients with systemic sclerosis (SS).[5-8] However, it is still controversial weather the

✉ Amra Adrovic
amra.adrovic@istanbul.edu.tr

Received 15th October 2020, revised 27th December 2020, accepted 6th April 2021.

signs of systemic sclerosis appear as a part of paraneoplastic syndrome or whether systemic sclerosis itself carries an increased risk for malignancies (lung cancer, gastric cancer, etc.). The possible association between systemic sclerosis and malignancy has been explained by a variety of theories, majority of them requiring further investigation and confirmation.[6-10]

Previously known as congenital cystic adenomatoid malformations (CCAM), the congenital pulmonary airway malformation (CPAM) represents localized developmental defects of airway formation at different times of lung development with an estimated incidence at 1:25,000 –1:35,000 births.[11] Previous studies showed that atypical goblet cell hyperplasia (AGCH) in CPAM represents a precursor lesion for pulmonary adenocarcinomas.[12,13]

In this report, we present a case with coincidental presence of two rare diseases: JSS and CPAM, an adolescent female patient admitted to hospital due to clinical signs of JSS. During the follow-up, the patient was diagnosed with cystic adenoid malformation of the lung. The pathophysiologic evaluation revealed mucinous adenocarcinoma. We sought to emphasize the importance of further evaluation of patients with JSS, especially those with negative autoantibodies.

Case Report

A 14- year-old female patient was admitted to our outpatient department due to swelling and stiffness of her fingers continuing for 2.5 years (Fig. 1). The patient was previously healthy with an unremarkable medical history. All complaints started 6 months prior to admission. At the physical examination, she had marked Raynaud's phenomenon on her fingers. The skin of the face looked "shiny and stiff". She had unremarkable initial laboratory test results: white blood cells count 4.900/mm^3, hemoglobin 13.1 gr/dl, thrombocytes count 244.000/ mm^3. Acute phase markers were in normal ranges: erythrocyte sedimentation rate 11 mm/h, CRP 0.04 mg/dl. The values of urea, creatinine, alanine-aminotransferase, aspartate-aminotransferase were in referent values. Evaluation of autoantibodies revealed the positivity of anti-nuclear antibody (ANA, >1/100), while anti-double strand DNA (ds-DNA), anti-Smith (Sm) and anti-Scl 70 antibodies were negative.

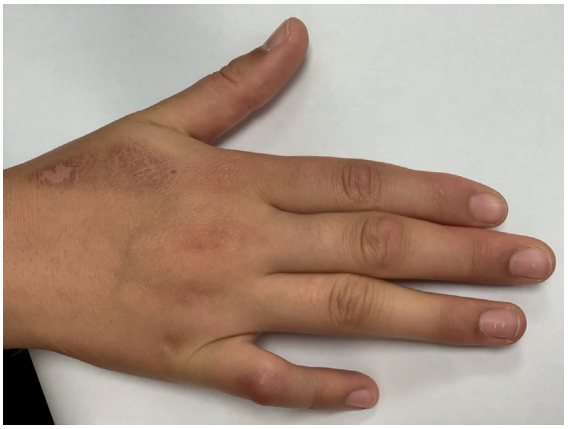


Fig. 1. Swelling of fingers, Gottron papules, Raynaud's phenomenon. Contracture in the proximal interphalangeal joint of the 5th finger of the right hand.

The patient was diagnosed with JSS according to Pediatric Rheumatology European Society (PReS)/American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for JSS[10] and prednisolone (10 mg/day, per oral) and methotrexate (15 mg/m^2/ week, subcutaneous) were started.

Lung involvement

Although the patient had no respiratory symptoms and her previous medical history was unremarkable, the evaluation of the respiratory system was performed as a part of the routine workup for JSS patients. During the regular screening for internal organ involvement, the chest X-ray and the spirometry were performed and found to be in the normal range with a forced vital capacity (FVC) of 80%, forced expiratory volume in 1 second (FEV1) 76%,

FEV1/FVC 92% and carbon-monoxide diffusion capacity (DLCO) 92%. The X-ray revealed a round shaped cystic lesion in the basal part of the left lung. The irregularity of the patient's X-ray was a reason to perform the thoracic high-resolution computerized tomography (HRCT) which revealed the cystic lesion (57 x 44 mm) in the basal part of the left lung lobe (Fig. 2). The left inferior lobectomy was performed.

Histopathological evaluation

Pathologic specimen demonstrated two focal mucinous adenocarcinoma (0.4 cm in diameter) with lepidic and focal acinar growth pattern without pleural invasion (Fig. 3A). Mucinous adenocarcinoma exhibited diffuse cytoplasmic expression for CK7 (Fig. 3B), CK20 staining was negative (Fig. 3C). The genetic analysis of the Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation revealed KRAS 12 (612C, 612S) positivity. The pathology report suggested congenital pulmonary airway malformation (CPAM type-2) as a basis for development of mucinous adenocarcinoma.

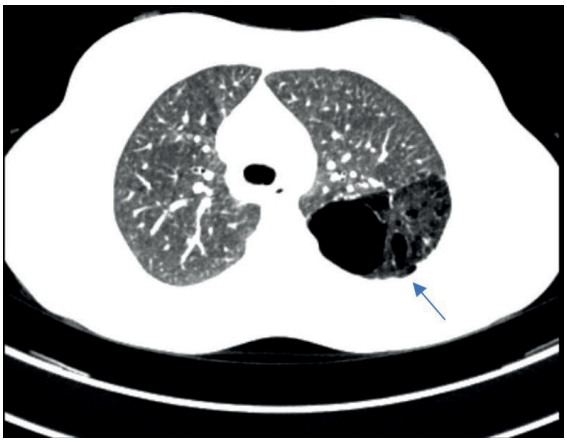


Fig. 2. Thoracic high-resolution computerized tomography (HRCT) of the patient showing cystic lesion (57 x 44 mm) in the basal part of the left lung lobe (arrow).

Follow-up

Considering the small size of malignant loci, the total resection of the tumor and absence of any sign for metastasis disease, adjuvant therapy was not scheduled and clinical surveillance with periodical thorax HRCT was planned. After 1.5 years of follow-up, at the last clinic visit, the patient had no complaints. The stiffness of the skin remarkably decreased modified Rodnan skin score (mRSS; 38 vs. 16). She had no signs of Raynaud phenomenon but still had puffy fingers in the physical examination with normal thoracic HRCT findings. The immunosuppressive treatment was continued during the 12 months after the surgical treatment. Due to regression of clinical findings (except for limited range of motion in the proximal interphalangeal joints in 4th and 5th fingers of the right arm, which are considered as disease sequela), the immunosuppressive treatment was canceled. Physiotherapy for her fingers continued.

Written consent to publish was obtained from the study participant.

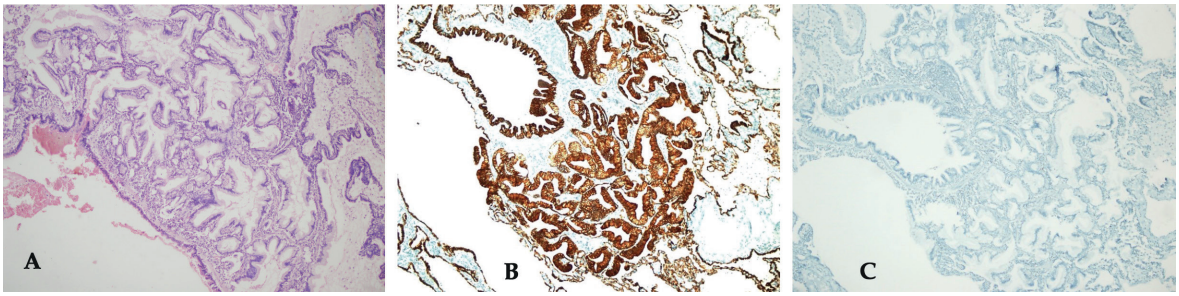


Fig. 3. Histopathological evaluation of the surgical material obtained by the left basal lobectomy. **A)** Mucinous proliferation composed of back-to-back glands, consistent with mucinous adenocarcinoma (arrows, H&E x100). **B)** Mucinous adenocarcinoma exhibiting diffuse cytoplasmic expression for CK7. **C)** CK20 staining was negative.

Discussion

This is the first report of a patient with JSS and congenital pulmonary airway malformation complicated by the mucinous adenocarcinoma of the lung.

The increased frequency of malignancy among patients with systemic sclerosis has been reported among adults.[6-9] Studies including pediatric patients are scarce due to rarity of the disease and the increased risk for cancers among children with JSS has not been reported yet.

The main dilemma regarding our patient was whether the lung mucinous adenocarcinoma as the complication of CPAM 2 represented the basis for clinical signs of JSS or the two conditions appeared coincidentally.

CPAM is a developmental disorder of the lung, characterized by the atypical cell hyperplasia which creates the ground for lung adenocarcinoma.[11-13] Fakler et al.[13] reported that 5 out of 33 CPAM patients developed lung adenocarcinoma. All of them had positive KRAS oncogenic mutation, which is considered to be an oncogenic driver in this patients' group.[13,14] Similarly, our patient had positive KRAS mutation which was confirmed in the cancer tissue.

In general, CPAM is a condition recognized early in childhood due to prominent respiratory symptoms including recurrent pulmonary infections, productive cough, and hemoptysis.[15-26] However, a certain number of patients remain asymptomatic until adulthood.[15,20,23,27] Frick et al. reported a 68-year-old male patient with invasive lung mucinous adenocarcinoma on the basis of CPAM.[17] The reported patient presented with chest pain but no systemic symptoms including signs of vasculopathy and systemic sclerosis were reported. Abecasis et al.[23] described an asymptomatic 14-year-old male patient who was coincidentally diagnosed with a mucinous bronchioloalveolar carcinoma associated with a CPAM type-1. The patient underwent right inferior lobectomy. After two years of follow-up he is completely asymptomatic and free of complications.

In a study by Pogoriler et al.[14], over a 2.5-year period 184 surgical specimens from 174 infants with congenital lung lesions were identified. No malignancy was identified. There were no cases of pleuropulmonary blastoma or acinar dysplasia.

Papagiannopoulos et al.[20] reported their 19-years' experience with cystic lesions of the lung among pediatric and adult population. A total of 46 operations were performed on 44 patients (24 children and 20 adults). Cystic adenomatoid malformation was the most common pathological finding. Malignancy was confirmed in three pediatric patients (12.5%): bronchoalveolar carcinoma in 2 and pleuropulmonary blastoma in 1 patient. In the adult population cystic adenomatoid malformation was the second most common lesion, seen in 5 (25%) patients. In half of the adults 11 (55%) were asymptomatic while the rest had signs and symptoms related to expansion or infection of the cysts. However, none of the adults had malignancy at the pathophysiological evaluation of the surgical specimen. Authors suggest resections of the congenital cysts in childhood, in order to avoid later complications, which could make operating more difficult.[20]

As we mentioned previously in the manuscript, our patients fulfilled PReS)/ACR/EULAR Classification Criteria for Juvenile Systemic Sclerosis.[10] She had proximal sclerosis and induration of the skin (initial mRSS 38), sclerodactyly, Raynaud's phenomenon and ANA positivity. The scleroderma specific anti Scl-70 was negative, but we should keep on mind the low percentage of its positivity in JSS patients. The acute phase markers and routine laboratory work-up was non-significant as it is in the majority of JSS patients.[1,3-5]

Bearing in mind the rarity of both conditions (JSS and mucinous adenocarcinoma associated

with CPAM) makes it inappropriate to consider both of them separately. Consequently, in our patient we prefer to consider JSS findings as a possible paraneoplastic sign of mucinous adenocarcinoma of the lung. Improvement of skin stiffness and disappearance of Raynaud's phenomenon after the resection of the tumor support our hypothesis.

Still, this is the first reported case which requires further confirmation by extending patient numbers. The other limitation is that the serologic evaluation of our patients has been limited since we were not able to perform analysis of tests which are associated to malignancy in systemic sclerosis.

As far as we know, this is the first report of patients with JSS with co-existing mucinous adenocarcinoma of the lung associated with cystic adenoid malformation. The underlying condition should be evaluated in patients with JSS, especially those with negative autoantibodies. Further studies with higher number of patients would reveal more relevant data.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AA, AAd, MY, ÖK; data collection: FH, OK, SŞ, KB; analysis and interpretation of results: AA, ŞB; draft manuscript preparation: AA, AAd, ÖK. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Zulian F, Cuffaro G, Sperotto F. Scleroderma in children: an update. Curr Opin Rheumatol 2013; 25: 643-50. https://doi.org/10.1097/BOR.0b013e3283641f61
2. Foeldvari I. Update on juvenile systemic sclerosis. Curr Rheumatol Rep 2015; 17: 18. https://doi.org/10.1007/s11926-014-0491-y
3. Adrovic A, Şahin S, Barut K, Kasapçopur Ö. Juvenile scleroderma: a referral center experience. Arch Rheumatol 2018; 33: 344-351. https://doi.org/10.5606/ArchRheumatol.2018.6578
4. Adrovic A, Sahin S, Barut K, Kasapcopur O. Juvenile scleroderma-what has changed in the meantime?. Curr Rheumatol Rev 2018; 14: 219-225. https://doi.org/10.2174/1573397114666180423105056
5. Foeldvari I, Klotsche J, Torok KS, et al. Are diffuse and limited juvenile systemic sclerosis different in clinical presentation? Clinical characteristics of a juvenile systemic sclerosis cohort. J Scleroderma Relat Disord 2018; 4: 49-61. https://doi.org/10.1177/2397198318790494
6. Shah AA, Rosen A. Cancer and systemic sclerosis: novel insights into pathogenesis and clinical implications. Curr Opin Rheumatol 2011; 23: 530-535. https://doi.org/10.1097/BOR.0b013e32834a5081
7. Olesen AB, Svaerke C, Farkas DK, Sorensen HT. Systemic sclerosis and the risk of cancer: a nationwide population-based cohort study. Br J Dermatol 2010; 163: 800-806. https://doi.org/10.1111/j.1365-2133.2010.09861.x
8. Bonifazi M, Tramacere I, Pomponio G, et al. Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies. Rheumatology 2012; 52: 143-154. https://doi.org/10.1093/rheumatology/kes303
9. Maria ATJ, Partouche L, Goulabchand R, et al. Intriguing relationships between cancer and systemic sclerosis: role of the immune system and other contributors. Front Immunol 2019; 9: 3112. https://doi.org/10.3389/fimmu.2018.03112
10. Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum 2007; 57: 203-212. https://doi.org/10.1002/art.22551
11. Stocker JT. Congenital pulmonary airway malformation: a new name and an expanded classification of congenital cystic adenomatoid malformation of the lung. Histopathol 2002; 41: 424-431.
12. Chang WC, Zhang YZ, Wolf JL, et al. Mucinous adenocarcinoma arising in congenital pulmonary airway malformation: clinicopathological analysis of 37 cases. Histopathology 2021; 78: 434-444. https://doi.org/10.1111/his.14239

13. Fakler F, Aykutlu U, Brcic L, et al. Atypical goblet cell hyperplasia occurs in CPAM 1, 2, and 3, and is a probable precursor lesion for childhood adenocarcinoma. Virchows Arch 2020; 476: 843-854. https://doi.org/10.1007/s00428-019-02732-4

14. Pogoriler J, Swarr D, Kreiger P, Adzick NS, Peranteau W. Congenital cystic lung lesions: redefining the natural distribution of subtypes and assessing the risk of malignancy. Am J Surg Pathol 2019; 43: 47-55. https://doi.org/10.1097/PAS.0000000000000992

15. Frick AE, Decaluwé H, Weynand B, Proesmans M, Van Raemdonck D. Invasive mucinous adenocarcinoma of the lung arising in a type 1 congenital pulmonary airway malformation in a 68-year-old patient: a case report. Acta Chir Belg 2021; 121: 55-60. https://doi.org/10.1080/00015458.2019.1634926

16. Soler-Perromat A, Vollmer I, Ramírez J, Sánchez M. Invasive mucinous adenocarcinoma in congenital pulmonary airway malformation: a case report. Arch Bronconeumol 2019; 55: 384-385. https://doi.org/10.1016/j.arbres.2018.12.001

17. Koh J, Jung E, Jang SJ, et al. Case of mucinous adenocarcinoma of the lung associated with congenital pulmonary airway malformation in a neonate. Korean J Pediatr 2018; 61: 30-34. https://doi.org/10.3345/kjp.2018.61.1.30

18. Ohye RG, Cohen DM, Caldwell S, Qualman SJ. Pediatric bronchioloalveolar carcinoma: a favorable pediatric malignancy?. J Pediatr Surg 1998; 33: 730-732. https://doi.org/10.1016/S0022-3468(98)90200-7

19. Granata C, Gambini C, Balducci T, et al. Bronchioloalveolar carcinoma arising in congenital cystic adenomatoid malformation in a child: a case report and review on malignancies originating in congenital cystic adenomatoid malformation. Pediatr Pulmonol 1998; 25: 62-66. https://doi.org/10.1002/(SICI)1099-0496(199801)25:1<62::AID-PPUL8>3.0.CO;2-Q

20. Papagiannopoulos K, Hughes S, Nicholson AG, Goldstraw P. Cystic lung lesions in the pediatric and adult population: surgical experience at the Brompton Hospital. Ann Thorac Surg 2002; 73: 1594-1598. https://doi.org/10.1016/S0003-4975(02)03469-0

21. Stacher E, Ullmann R, Halbwedl I, et al. Atypical goblet cell hyperplasia in congenital cystic adenomatoid malformation as a possible preneoplasia for pulmonary adenocarcinoma in childhood: a genetic analysis. Hum Pathol 2004; 35: 565-570. https://doi.org/10.1016/j.humpath.2004.01.008

22. Ioachimescu OC, Mehta AC. From cystic pulmonary airway malformation, to bronchioloalveolar carcinoma and adenocarcinoma of the lung. Eur Respir J 2005; 26: 1181-1187. https://doi.org/10.1183/09031936.05.00011705

23. Abecasis F, Gomes Ferreira M, Oliveira A, Vaz Velho H. Bronchioloalveolar carcinoma associated with congenital pulmonary airway malformation in an asymptomatic adolescent. Rev Port Pneumol 2008; 14: 285-290. https://doi.org/10.1016/S0873-2159(15)30236-1

24. Giubergia V, Barrenechea M, Siminovich M, Pena HG, Murtagh P. Congenital cystic adenomatoid malformation: clinical features, pathological concepts and management in 172 cases. J Pediatr (Rio J) 2012; 88: 143-148. https://doi.org/10.2223/JPED.2177

25. Li J, Chen GS, Zhang X, Moore L, Cheng H. Congenital cystic adenomatoid malformation with associated mucinous bronchioloalveolar carcinoma in a neonate. Fetal Pediatr Pathol 2014; 33: 29-34. https://doi.org/10.3109/15513815.2013.842272

26. Balkanlı S, Özturk MA, Köse M, et al. A report of adenocarcinoma in situ and congenital pulmonary airway malformation in a three-day-old infant with a review of the literature. Turk J Pediatr 2014; 56: 299-302.

27. Ribet ME, Copin MC, Soots JG, Gosselin BH. Bronchioloalveolar carcinoma and congenital cystic adenomatoid malformation. Ann Thorac Surg 1995; 60: 1126-1128. https://doi.org/10.1016/0003-4975(95)00494-6