Adolescent-Onset Anti-MDA5 Antibody-Positive Juvenile Dermatomyositis with Rapidly Progressive Interstitial Lung Disease and Spontaneous Pneumomediastinum: A Case Report and Literature Review

Tsz Wing Yeung (yeungtw@ha.org.hk)
Hong Kong Children's Hospital https://orcid.org/0000-0003-0495-1332
Kai Ning Cheong
Hong Kong Children's Hospital
Yu Lung Lau
Hong Kong University: University of Hong Kong
Kei Chiu Niko Tse
Tuen Mun Hospital

Case Report

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Abstract

Background:

Dermatomyositis with positive anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody has a distinct phenotype associated with small hand joint arthritis, mucocutaneous ulceration, and less muscle involvement. It is reported to be associated with rapidly progressive interstitial lung disease (RP-ILD) and have a high mortality rate in adult studies. There is evidence that cases complicated with spontaneous pneumomediastinum (PNM) have an increase in mortality. Most of the evidence of this rare disease is derived from adult studies. We report a case in adolescent age complicated with both RP-ILD and PNM with a good disease outcome after aggressive immunosuppressive therapy. We illustrate the diagnostic challenge and the importance of test for the myositis-associated antibodies (MSA).

Case presentation:

A 16-year-old Chinese female presented with fever and cough for one day, and finger swelling for three weeks. Physical examination revealed arthritis of fingers and wrists, ulcers and palmar papules over fingers, hyperpigmentation of interphalangeal joints, rash over the neck and calcinosis over external ears. The diagnosis of dermatomyositis was made one month later until the onset of malar rash, Gottron's papules and myalgia. The diagnosis was supported by the presence of anti-MDA5 antibody and evidence of inflammatory myopathy on magnetic resonance imaging without performing muscle biopsy or electromyography. In retrospect, she already had interstitial lung disease at first presentation manifested as cough and opacity on chest radiograph, which was later confirmed with chest computed tomography and pulmonary function test. She was treated according to adult guidelines with calcineurin inhibitor and steroid. Her disease was steroid-resistant, which was complicated with RP-ILD and spontaneous PNM. Intensive immunosuppressive therapy including cyclophosphamide and rituximab were required to induce remission.

Conclusions:

Recognition of distinct clinical features including mucocutaneous ulceration and test for MSA are important for prompt diagnosis of anti-MDA5 antibody-positive dermatomyositis, as early aggressive treatment and anticipation of complications could make a difference in the outcome of this disease with high mortality.

Background

Juvenile dermatomyositis (JDM) is a systemic inflammatory disease characterized by typical cutaneous lesions including Gottron's papules and heliotrope rash, and proximal muscle weakness with age of onset under 18-year-olds. It is a rare disease that affects 2–4 per million of children each year [1]. The anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody was identified in 2005 to associate with clinically amyopathic dermatomyositis (CADM) and rapidly progressive interstitial lung disease (RP-

ILD) in adults [2, 3]. CADM is a type of dermatomyositis with predominant cutaneous lesions without muscle weakness, although laboratory or radiological evidence of myositis can be present [4]. RP-ILD is defined as progressive interstitial lung disease (ILD) within three months of the onset of respiratory symptoms [5]. There is increasing awareness of this disease entity due to its lower six-month survival rate: 57% in anti-MDA5 antibody-positive dermatomyositis as compared to 98% in those without the antibody [6]. We report a case of anti-MDA5 antibody-positive JDM with RP-ILD and spontaneous pneumomediastinum (PNM).

Case Presentation

A 16-year-old Chinese female with no significant past medical history presented with one-day history of low-grade fever and cough. She also complained of painful swelling of fingers for three weeks. Physical examination revealed dactylitis of all fingers, arthritis of both wrists, small ulcers mainly over finger pulps and periungual regions, papules over palmar surface of fingers, erythematous plaques over the neck and calcinosis over external ears (Fig. 1, 2). There was hyperpigmentation over the dorsal surface of interphalangeal joints, but no definite Gottron's papules. She had no muscle weakness. Physical examination was otherwise unremarkable. Blood creatine kinase (CK) level was normal at 129 U/L (normal range 37–173 U/L). Chest radiograph showed left perihilar opacity. She was treated for pneumonia and arthritis before being discharged with a course of amoxicillin/clavulanate and naproxen.

Upon follow-up examination one month later, she complained of persistent cough and presented new symptoms including muscle pain over proximal limbs and oral ulcers. Examination showed malar rash, Gottron's papules (Fig. 1) and bilateral crepitation at lung bases. She had mild proximal weakness over lower limbs only, which could be explained by myalgia. Nail fold capillaroscopy showed frequent giant capillaries and capillary microhemorrhages. Blood test showed elevated CK at 858 U/L and ferritin at 2006 pmol/L (Fig. 3). Anti-nuclear antibody and Anti-Ro52 antibody were positive. Anti-MDA5 antibody was detected in the myositis-specific antibody (MSA) panel, but quantitative test for the antibody was not available. Chest computed tomography (CT) showed multiple subpleural and peripherally located consolidations in both lungs (Fig. 4). No infective organism was isolated from bronchoalveolar lavage. Pulmonary function test showed reduced diffusing capacity for carbon monoxide (DLCO) to 59% of the predicted value. Magnetic resonance imaging (MRI) of pelvis and thighs showed T2-weighted hyperintensity over bilateral pelvic and thigh muscles, consistent with systemic inflammatory myopathy. A diagnosis of JDM with ILD was made without muscle biopsy.

She received a 3-day course of pulse methylprednisolone at 1 g/day, followed by a combination of prednisolone of 1 mg/kg/day and tacrolimus. There was an initial improvement with resolved dactylitis and decreasing blood CK level (Fig. 3). Two weeks later, the patient developed hoarseness of voice, shortness of breath on exertion, and new vasculitic ulcers over fingers. Her muscle power deteriorated to Medical Research Council grade 3 to 4, with rebound of blood CK level. Videofluoroscopic swallowing study showed mild pharyngeal dysphagia. A 3-day course of pulse methylprednisolone at 500 mg/day and mycophenolate mofetil (MMF) were added in view of the deterioration.

At week three of treatment, she complained of neck and chest pain. Diffuse neck swelling was noted with crepitus at the anterior neck. Chest radiograph showed subcutaneous emphysema over the cervical region and PNM. Chest CT showed an increase in consolidative changes in addition to PNM. Combination of rituximab (1 g each on day 1 and day 15), intravenous immunoglobulin (IVIG) (2 g/kg biweekly for 4 doses, then 4-weekly for one year) and intravenous cyclophosphamide (4-weekly for 6 doses, cumulative dose 5.75 g/m^2) were given. Two doses of oral methotrexate (MTX) were given but discontinued due to elevated alanine transaminase (ALT) up to 400 U/L. Prescription of tacrolimus was stopped to avoid over-immunosuppression.

With oxygen supplement, PNM resolved one month later. After two months of aggressive treatment, digital ulcers, cough, hoarseness and muscle weakness were completely resolved. Follow up chest CT after two months showed interval resolution of consolidative changes which replaced by fibrosis. MTX was reintroduced after ALT normalized, and the dose of prednisolone was tapering off. Follow-up pulmonary function test eight months from diagnosis showed improved DLCO to 80% of the predicted value. At her follow-up 1 year from diagnosis, she had no recurrence while on prednisolone 5 mg daily, maintenance MMF, MTX and monthly IVIG. She did not experience severe side effects such as marrow suppression or severe infection other than elevated intraocular pressure, which was controlled by timolol eye drops.

Discussion

Dermatomyositis with positive anti-MDA5 antibody has a distinct phenotype in terms of skin, joint, muscle, and lung involvement in both children and adults. It is associated with mucocutaneous ulceration, symmetrical polyarthritis of small joints of the hands. It is also found to be associated with painful palmar papules in adults [7–9]. For muscle involvement, most adult patients are clinically amyopathic, although the distribution varies with the ethnic group where CADM occurred in 82% of Japanese and 45% of Caucasian [6, 10]. CADM was not commonly reported in JDM with anti-MDA5 antibody, but it has a milder muscle involvement compared to those without [7]. For lung involvement, ILD overall occurs rarely in only 8% of JDM [11], while it occurs at a higher frequency in those with anti-MDA5 antibody. In a Japanese study, all 11 out of 35 JDM patients (31%) who possessed the antibody had ILD, of whom 6 had RP-ILD. It was concluded that JDM patients with the antibody were significantly more likely to have RP-ILD [12]. Ethnic difference in the severity of ILD in anti-MDA5 antibody-positive dermatomyositis is observed, where ILD is in general not rapidly progressive in Caucasians in both children and adults [7, 10].

It was a diagnostic challenge with our patient's presenting symptoms mimicking juvenile idiopathic arthritis or vasculitis, leading to a one-month delay in diagnosis as pathognomonic cutaneous features and muscle weakness did not appear at first presentation. In retrospect, the patient was first presented with the typical phenotype of anti-MDA5 antibody-positive dermatomyositis with cutaneous ulceration, palmar papules, and small hand joint arthritis. Other than these features, the interphalangeal joint hyperpigmentation and calcinosis over external ears should alert one to dermatomyositis. An awareness

of less common signs of dermatomyositis and a high index of suspicion are required to make the diagnosis. The diagnosis of dermatomyositis in our patient was supported by positive anti-MDA5 antibody and evidence of inflammatory myopathy on MRI without performing muscle biopsy and electromyography described in the widely used Bohan and Peter's criteria [13]. Anti-MDA5 antibody is one of the MSA that is dermatomyositis-specific, which is not found in other inflammatory myopathies or connective tissue disorders [2, 8]. Although negative MSA does not exclude the diagnosis, the test is non-invasive and is helpful in patients with cutaneous features not specific to dermatomyositis. Anti-MDA5 antibody is particularly important to be performed in patients presenting with skin ulcers of unknown diagnosis even without muscle weakness because of its essential prognostic value. Referencing on the high mortality rate due to respiratory failure in RP-ILD from adult data, one can anticipate a rapid disease progression and complications in those with positive anti-MDA5 antibody. It is valuable as ILD can occur very early in the disease course as in our patient, where an early diagnosis allows a window for aggressive treatment such that progression into RP-ILD may be avoided. New classification criteria by the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) for adult and juvenile idiopathic inflammatory myopathies were recently published, in an effort to include one MSA – anti-Jo1 antibody [14]. It is expected that other MSA may be incorporated in the classification criteria in the future after MSA is more widely used.

Due to rarity of the disease hence a lack of randomized controlled trials, the current treatment for JDM is largely based on consensus guidelines. The treatment for JDM with ILD or anti-MDA5 antibody is not well established. It could also be attributed to the lack of ILD grading parameters to guide further studies. In 2010, the Childhood Arthritis & Rheumatology Research Alliance (CARRA) in North America reached consensus on the treatment of moderately severe JDM, using a combination of steroid and MTX with or without IVIG [15]; however patients with pulmonary involvement and skin ulceration were excluded. In 2017, the Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative proposed a treatment recommendation for JDM with major organ involvement, using cyclophosphamide in addition to steroid and MTX, and consider the use of IVIG, cyclosporine A, infliximab, rituximab etc. in cases with poor response [16]. However, the decision to intensify treatment is based solely on clinician's opinion. Owing to high mortality, treatment for anti-MDA5 antibody-positive JDM should be individualized as early intensification of therapy in those with a poor response may be vital. In adults, the recommended initial treatment for ILD with anti-MDA5 antibody is at least dual therapy with steroid and calcineurin inhibitor with or without cyclophosphamide [17, 18]. We followed this recommendation as the patient was in her adolescence and the fact that there was a lack of paediatric recommendation. It has been debated whether to use cyclophosphamide in view of the risk of gonadotoxicity for young females. However, her disease was steroid-resistant with rapid progression of ILD and was complicated with PNM. It was alarming as a recent study suggested that PNM in adult anti-MDA5 antibody-positive dermatomyositis patients was associated with significantly higher mortality [19]. Multiple immunosuppressants including cyclophosphamide and rituximab were required to induce disease remission. It is difficult to conclude the efficacy of rituximab, a chimeric monoclonal anti-CD20 antibody that depletes B-cell, as multiple agents

were added in proximity. The use of rituximab in RP-ILD with positive anti-MDA5 antibody appeared promising in an adult case series [20], however there are few reports on its use in paediatric groups.

To improve the survival rate of refractory dermatomyositis, there is a need for novel mechanism-based treatment in the era of molecular medicine. It has been reported that the type I interferon (IFN) pathway is involved in the pathogenesis of juvenile and adult dermatomyositis [21]. Ladislau et al. demonstrated in 2018 that type I IFN pathway activation *in vitro* reproduces the main dermatomyositis pathological findings including muscle atrophy and vasculopathy, and the pathogenic effects i*n vitro* were abolished by a Janus kinase (JAK) inhibitor ruxolitinib that targets the IFN pathway [22]. Sabbagh et al. in 2019 reported the use of tofacitinib, a JAK inhibitor, leading to clinical improvement within six months in two anti-MDA5 antibody-positive JDM refractory to multiple agents including rituximab [23]. Further studies are required to shed light on the use of JAK inhibitor as adjuvant or rescue treatment for this subset of JDM.

Conclusion

In conclusion, physicians have to be aware of the phenotype of anti-MDA5 antibody-positive dermatomyositis. Test for MSA including anti-MDA5 antibody has been crucial in patients with skin ulcers of unknown diagnosis, as early diagnosis and treatment of this rare but severe disease makes a difference in the outcome. In view of poor prognosis of the disease, further studies will be necessary to explore the optimal treatment for anti-MDA5 antibody-positive dermatomyositis in the paediatric group.

Abbreviations

Anti-MDA5
Anti-melanoma differentiation-associated gene 5; JDM:Juvenile dermatomyositis; RP-ILD:Rapidly progressive interstitial lung disease; ILD:Interstitial lung disease; PNM:Pneumomediastinum; MSA:Myositis-specific antibodies; CADM:Clinically amyopathic dermatomyositis; CK:Creatine kinase; CT:Computed tomography; DLCO:Diffusing capacity for carbon monoxide; MRI:Magnetic resonance imaging; MMF:Mycophenolate mofetil; IVIG:Intravenous immunoglobulin; MTX:Methotrexate; ALT:Alanine transaminase; IFN:Interferon; JAK:Janus kinase

Declarations

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TWY collected data, drafted and revised the manuscript. KNC, YLL, KCNT reviewed and supervised the writing of the manuscript. All authors read and approved the final manuscript.

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Competing interests:

The authors declare that they have no competing interests

Author details:

[1]Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Hong Kong SAR

[2]Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong SAR

[3]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong SAR

[4]Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong SAR

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Figures

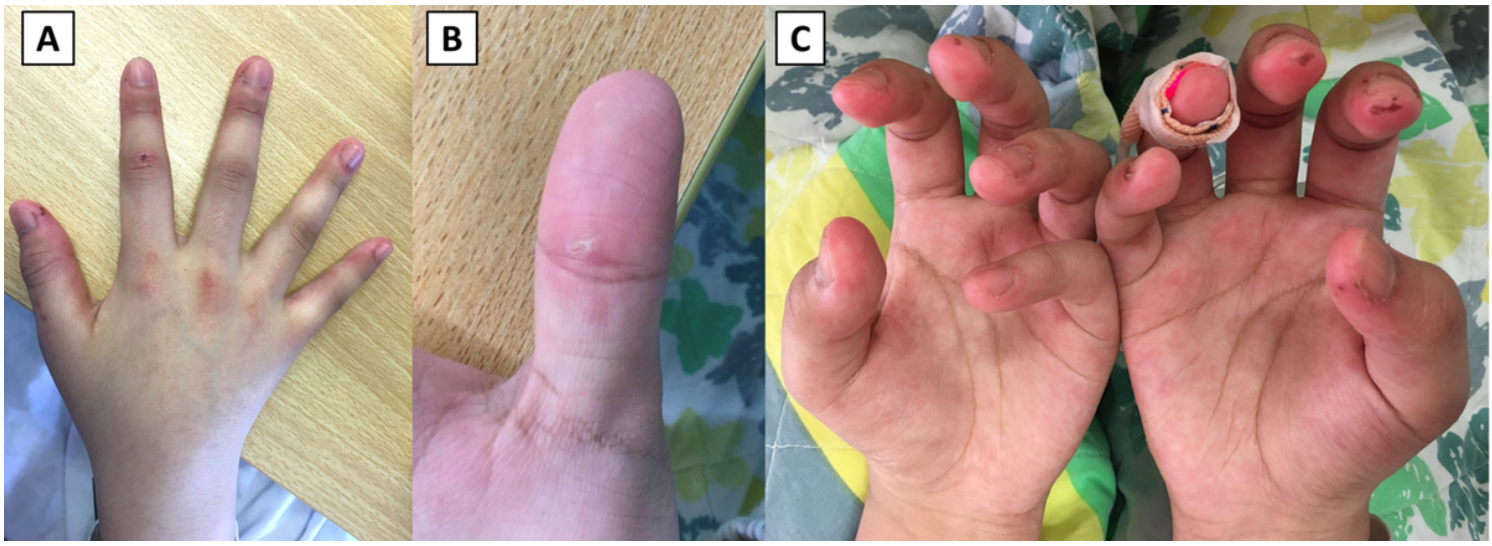

Figure 1

Cutaneous and skeletal features of the patient. A Gottron's papules, interphalangeal joint hyperpigmentation, dactylitis, and skin ulcers. B A palmar papule over the thumb. C Skin ulcers over finger pulps.

Figure 2

Calcinosis over the external ear.

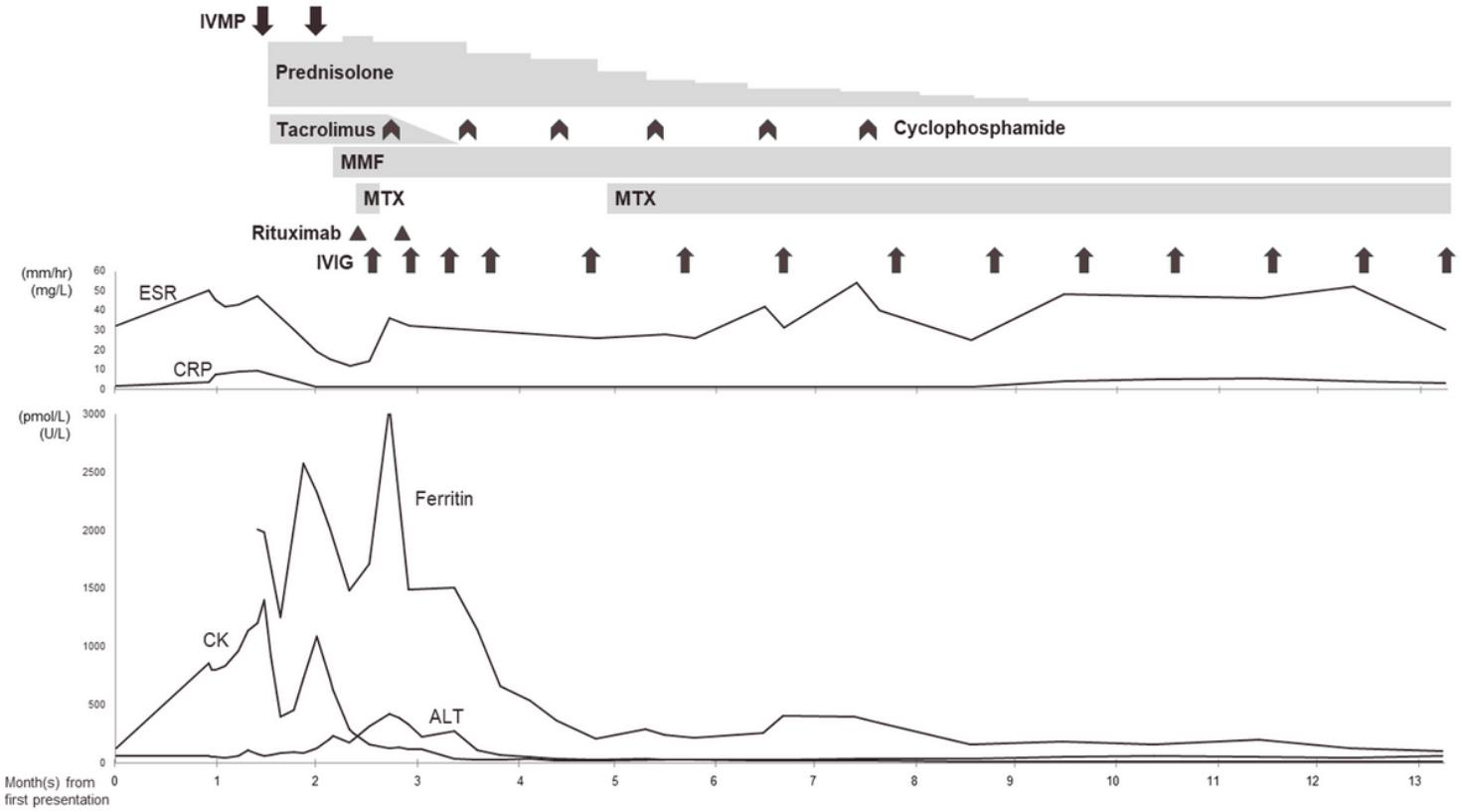

Figure 3

Laboratory results during treatment. IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; MTX, methotrexate; IVIG, intravenous immunoglobulin; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; CK, creatine kinase; ALT, alanine aminotransferase.

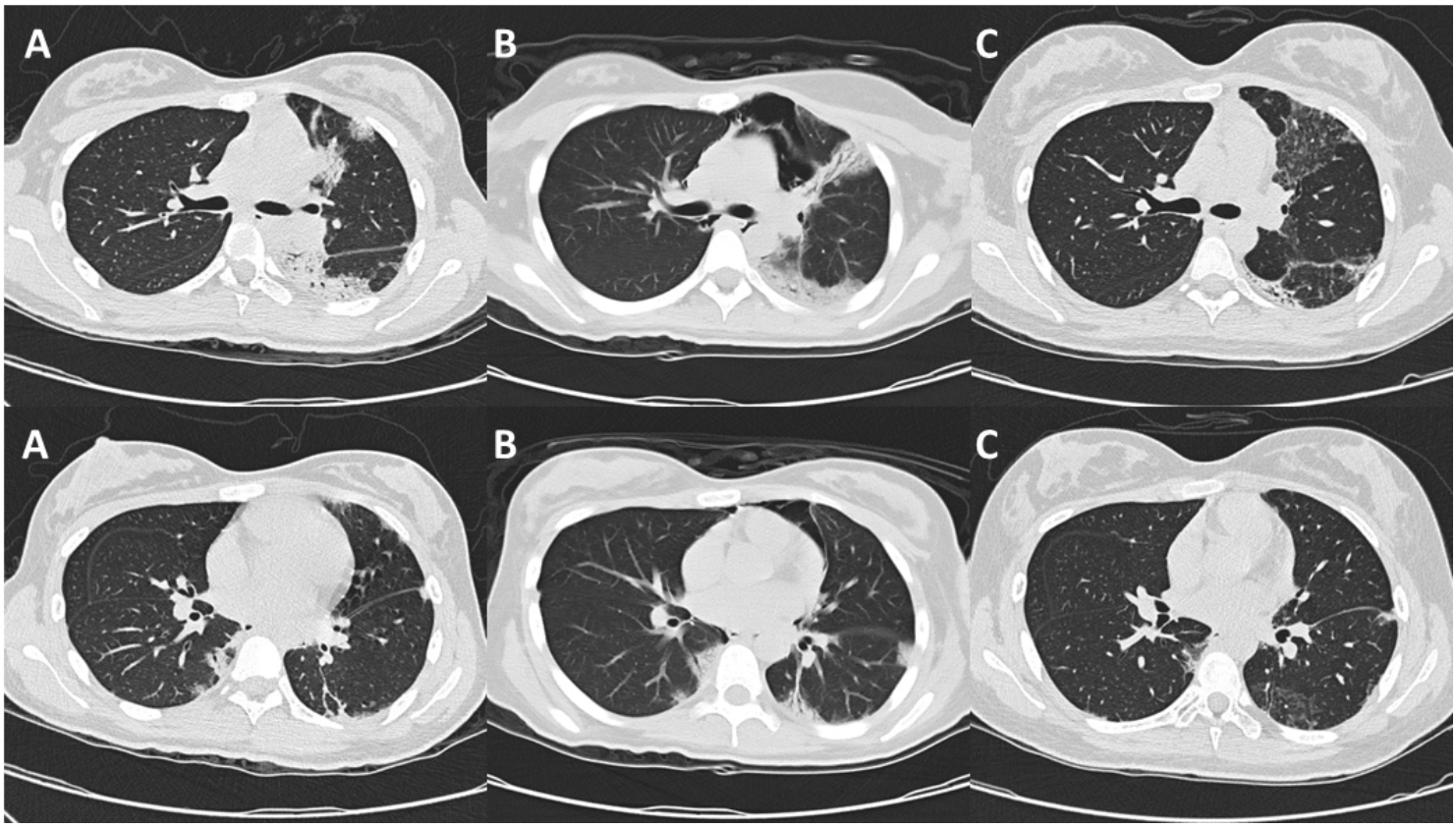

Figure 4

Serial chest computer tomographies of the patient. A Subpleural consolidation of lungs at diagnosis. B Pneumomediastinum and increase in consolidation 3 weeks after treatment. C Resolution of consolidation with fibrosis after rituximab and 3 cycles of cyclophosphamide.