Case report

Acute hypoxic respiratory failure secondary to antisynthetase syndrome: A case report and review of literature

Michelle Cancel (M.D.)*, Mingchen Song (M.D.)

SIU School of Medicine Division of Pulmonology and Critical Care Medicine, United States

ARTICLE INFO

Keywords:
Antisynthetase syndrome
Interstitial lung disease

ABSTRACT

Objective: Antisynthetase syndrome is a condition that includes interstitial lung disease and inflammatory myositis in its definition. The interstitial lung disease of this syndrome can vary in severity and if not identified soon enough, can lead to severe respiratory failure. Here we present a patient who had a working diagnosis of acute eosinophilic pneumonia. He initially improved after prolonged hospitalization and course of high dose steroids. CT chest revealed interval improvement in his bilateral ground glass and reticular opacities but residual fibrotic interstitial lung disease. However, he decompensated subsequently with relapsed hypoxia during activity. We hope that this review will bring awareness to antisynthetase syndrome and provide tools for earlier diagnosis and treatment. The primary objective of this study was to review presenting symptoms, diagnosis, treatment and outcomes. This review is unique because we focused on antisynthetase syndrome that initially manifested with lung symptoms rather than myositis or skin changes.

Methods: We have performed a comprehensive review of 30 cases of antisynthetase syndrome in the literature (including our case).

Results: Total 30 cases reported, 17 male patients and 13 female patients. Only 43% of the cases presented with lung symptoms alone, while 57% of the cases presented with lung and muscle symptoms simultaneously.

Conclusion: This supports the fact that antisynthetase syndrome most commonly presents with lung and muscle manifestations simultaneously. The fact that our case presented with lung findings alone led to the delay in his diagnosis.

1. Introduction

Antisynthetase syndrome is a rare but significant cause of interstitial lung disease. It most commonly presents in middle-aged women. The triad of antisynthetase syndrome includes interstitial lung disease, inflammatory myositis and presence of antisynthetase antibodies (aminoacyl-transfer RNA synthetase antibodies). These antibodies are directed against enzymes that attach amino acids to their associated transfer ribonucleic acid during polypeptide synthesis. So far, 8 different antibodies have been identified [1]. The most common antibody is Anti-Jo-1, next are anti-PL-7 and anti-PL-12 [2]. These are associated with histidine, threonine and alanine respectively [3]. Anti-Jo-1 antibody is named after a patient affected with interstitial lung disease and polymyositis by scientists in 1980. When a patient has one of these antibodies it is highly specific for antisynthetase syndrome. Antisynthetase syndrome is known for its acute disease onset but is most often a delayed diagnosis. The delay in diagnosis stems from varying degrees of symptomatology and features that are in common with other forms of interstitial lung disease (ILD). Early diagnosis can improve outcomes of this disease. We report a case of antisynthetase syndrome in which the patient presented with solely pulmonary symptoms (see Fig. 1).

2. Case presentation

The patient is a 61 year old male who presented to an outside facility with productive cough, dyspnea and pleuritic chest pain of one month duration. No rash or joint pain were described. Past medical history included hypertension and regular alcohol use. Patient was a former smoker and worked at a printing company. He denied any exposure to dust or fumes at his job. He reported that he was building a wood shelter for hunting outside when he began to have a dry cough and dyspnea. He was given oral antibiotics and prednisone by his primary care doctor but his symptoms did not improve. His vitals on initial
presentation were notable for hypoxia to 80% on room air. Lung exam was notable for bilateral infrascapular crackles and bronchial breath sounds. He had a respiratory alkalosis and hypoxia with pH 7.49, PCO₂ 31.3 mmHg, HCO₃ 24.8 mEq/L, PO₂ 61.6 mmHg. CT angiography of the chest revealed patchy bibasilar opacities, scattered bilateral ground glass and nodular opacities but no pulmonary embolism. He was started on broad spectrum antibiotics (IV vancomycin, piperacillin-tazobactam, levofloxacin) and continued on them after transfer to our facility.

Infectious workup was largely negative. Influenza PCR was negative. Blood cultures, sputum culture, lactic acid, procalcitonin, urinalysis were all negative. Legionella, Mycoplasma, Histoplasmosis, Coccidioides, Aspergillosis and Chlamydia pneumonia studies were negative. Patient had a negative ANCA but positive ANA (1:40). Briefly after admission to our facility, patient had continued hypoxia on 15 L nonrebreather mask. He was subsequently transferred to the ICU, intubated and placed on mechanical ventilation. ICU stay was complicated by acute kidney injury and hypotension. After 3 days of broad spectrum antibiotics and no improvement, as well as negative cultures, patient was started on itraconazole 200 mg three times daily for fungal coverage. Bronchoscopy was done and revealed increased eosinophils in bronchoalveolar lavage (BAL), concerning for eosinophilic pneumonia. He was started on IV methylprednisolone 60 mg every 6 hours for 3 days then to a target dose of 175 mg. He was started on oral prednisone taper initiated during his initial hospitalization. Additional therapy was warranted due to his symptoms, which included hypoxia and severe restrictive lung disease. Cyclophosphamide was initiated, with dosing of 100 mg each morning for 3 days, 150 mg each morning for 3 days then to a target dose of 175 mg. He was started on oral sulfa-methoxazole-trimethoprim double-strength 160–800 mg qday for Pneumocystis jiroveci pneumonia (PJP) prophylaxis. He continues to follow with his physicians at the tertiary care center. Patient was on cyclophosphamide for 6 months and has now transitioned to mycophenolate. He was weaned off oxygen after initiation of cyclophosphamide. He reports that he is now playing golf again without difficulty (see Table 1).

3. Materials and methods

Ethics board approval was waived because research was not done on active human participants. We obtained our patient’s written consent to publish this material, including his case presentation, hospital course and treatment outcomes as described. We used PubMed and the American College of Chest Physicians for our online literature search. We reviewed 30 cases of antisynthetase syndrome in the literature (including our case). Inclusion criteria included lung symptoms as an initial presenting symptom. We excluded studies that had muscle symptoms alone and cases without any lung symptoms at all. Characteristics from each paper including demographics, presentation, symptoms, imaging, serologic tests, diagnosis, treatment and outcomes were compiled into Table 2.

4. Results

We completed a comprehensive review of 30 cases of antisynthetase syndrome in the literature (including our case). Total 30 cases reported, 17 male patients and 13 female patients. Only 43% of the cases...
presented with lung symptoms alone [2,4,7,10,16–18,23–25,29,32], while 57% of the cases presented with lung and muscle symptoms simultaneously [1,5,8,11–15,19–22,26–28,30,31]. We did not review any cases that presented with muscle symptoms alone. This supports the fact that antisynthetase syndrome most commonly presents with lung and muscle manifestations simultaneously. The fact that our case was not a case that presented with muscle symptoms alone. This supports the fact that antisynthetase syndrome most commonly presents with lung and muscle symptoms simultaneously. The fact that antisynthetase syndrome most commonly presents with lung and muscle symptoms simultaneously.

### Table 1

| Findings on CT of the chest | Pre-Bronchodilator | Post-Bronchodilator |
|----------------------------|---------------------|---------------------|
| Bilateral lung infiltrates  | 30/30 (100%)        |                     |
| Ground glass opacities     | 18/30 (60%)         |                     |
| Traction bronchiectasis    | 8/30 (27%)          |                     |
| **Serologic tests**        |                     |                     |
| ANA                        | 11/30 (37%)         |                     |
| Anti-Jo-1                  | 18/30 (60%)         |                     |
| Anti-Ro                    | 7/30 (23%)          |                     |
| Anti-CCP                   | 3/30 (10%)          |                     |
| Rheumatoid factor          | 5/30 (17%)          |                     |
| Anti-PL-7                  | 7/30 (23%)          |                     |
| Anti-PL-12                 | 3/30 (10%)          |                     |
| Muscle biopsy              | 8/30 (27%)          |                     |
| Lung biopsy                | 10/30 (33%)         |                     |
| Skin biopsy                | 2/30 (7%)           |                     |
| **Treatment**              | Steroids            | 29/30 (97%)         |
|                           | Cyclophosphamide    | 11/30 (37%)         |
|                           | Azathioprine        | 3/30 (10%)          |
|                           | Mycophenolate Mofetil | 8/30 (27%)   |
|                           | Methotrexate        | 3/30 (10%)          |
|                           | Rituximab           | 4/30 (13%)          |
|                           | Tacrolimus          | 3/30 (10%)          |
| **Outcomes**               | Resolved            | 3/30 (10%)          |
|                           | Improved            | 23/30 (77%)         |
|                           | Not disclosed        | 3/30 (10%)          |
|                           | Expired             | 1/30 (3%)           |
| **Markers of improvement** | Resolution of symptoms | 11/26 (42%) |
|                           | Decreased inflammatory markers | 3/26 (12%) |
|                           | Clearance of infiltrates on chest imaging | 2/26 (8%) |
|                           | Combination of the above 3 | 10/26 (38%) |

5. **Discussion**

Clinicians should be aware of antisynthetase syndrome and its manifestation. This case is an example of how a broad differential diagnosis should be considered, especially when patients do not respond to standard therapy [4]. In a patient with acute onset pneumonia and respiratory distress, the more common etiologies should be worked up first. However, if workup for bacterial, fungal and viral etiologies come up negative, autoimmune and inflammatory conditions should remain on the differential. Diagnostic criteria for antisynthetase syndrome includes a positive anti-aminoacyl-tRNA antibody along with 2 of the three following: interstitial lung disease, inflammatory myopathy, inflammatory polyarthritis. There are multiple patterns of interstitial lung disease in antisynthetase syndrome. These include nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), diffuse alveolar damage (DAD), organizing pneumonia (OP) and acute interstitial pneumonia (AIP) [5]. NSIP is the most common in antisynthetase syndrome [6]. DAD is the characteristic pneumonia of eosinophilic pneumonitis. Diagnosis is most commonly made by antibody testing, high resolution CT scan, lung biopsy or any combination of the three. Biopsy may be limited by patient's clinical condition. High resolution CT scan of the chest is most commonly done when interstitial lung disease is suspected. The most common findings on CT scan include
ground glass opacifications, peribronchial consolidations and find nodularity [7]. Fibrosis is a negative prognostic indicator in antisynthetase syndrome [8].

Treatment modalities vary depending on the severity of the patient's interstitial lung disease. This is reflected in imaging, PFTs and clinical symptoms. Muscle and bone involvement does not necessarily correlate with disease severity. Systemic glucocorticoids (IV or oral) are first-line treatment. If respiratory failure continues to worsen on steroids, patients require other types of immunosuppression for treatment. Options include azathioprine, mycophenolate mofetil and cyclophosphamide.

One important thing to note is the patient's level of thiopurine methyltransferase. Mycophenolate is favored in patients with a low level of thiopurine methyltransferase. The prognosis of antisynthetase syndrome is not widely studied. However, it is thought that with rapid diagnosis and treatment along with close monitoring, patients can make a full recovery. Antisynthetase syndrome and eosinophilic pneumonia are extremely similar with regards to symptoms, imaging studies, laboratory testing as well as diagnostic studies, including bronchoalveolar lavage. This was demonstrated in the diagnostic process of our patient case.

We had several limitations that contributed to our delay in diagnosis. These included low prevalence of antisynthetase syndrome in our patient population, lack of knowledge with the diagnostic criteria and treatment modalities and an initial working diagnosis that caused investigation into other etiologies. Patient had an initial delay in his diagnosis, about 4–5 months, because of our inability to recognize antisynthetase syndrome. While the patient improved clinically after referral to another facility, this delay in diagnosis prompted us to look at how we evaluate patients who come in with acute hypoxic respiratory failure.

Antisynthetase syndrome is a complex autoimmune disorder diagnosed and treated by Pulmonologists and Rheumatologists. Official diagnostic criteria may not be established, and many centers may not have the ability to test for antisynthetase antibodies. However, we believe that this review of literature will provide the knowledge and tools for clinicians to identify and treat antisynthetase syndrome.

6. Conclusion

Antisynthetase syndrome should always be considered when treating a patient for acute respiratory failure with characteristics of interstitial lung disease. Our patient's disease process and time until treatment with adequate immunosuppression was prolonged due to delay of diagnosis. We anticipate that as the awareness of this syndrome grows and more research is completed, this can help guide recognition, diagnosis and treatment of antisynthetase syndrome.

Conflicts of interest

We have no conflicts of interest to disclose. Ethics board approval was waived because research was not done on active human participants. We obtained our patient's written consent to publish this material, including his case presentation, hospital course and treatment outcomes as described. We used PubMed and the American College of Chest Physicians for our online literature search. We reviewed 30 cases of antisynthetase syndrome in the literature (including our case).

References

[1] E. De Langhe, J. Lenaerts, X. Bossuyt, R. Westhovens, W. Wuyts, Mechanic's hands in a woman with undifferentiated connective tissue disease and interstitial lung disease - anti-PL-7 positive antisynthetase syndrome: a case report, J. Med. Case Rep. 9 (82) (2015 April 15) (Epub ahead of print).
[2] A. Shah, S. Patel, Acute onset antisynthetase syndrome with pericardial effusion and non-specific interstitial pneumonia, J. Clin. Med. Res. 9 (2016) 683–687.
[3] A. Cavalcante Espósito, H. Miot, T. Gige, Syndrome in question: antisynthetase syndrome (Anti-PL-7), An. Bras. Dermatol. 91 (2016) 683–685.
[4] Q. Haydour, M. Wells, S. McCoy, E. Nelsen, P. Escalante, E. Matteson, Antisynthetase syndrome presenting as cryptogenic organizing pneumonia, Respir. Med. Case Rep. 6 (2012) 13–15.
[5] S. Priyangika, W. Karunaratna, J. Liyanage, M. Gunawardana, S. Udumalgala, C. Rosa, et al., Organizing pneumonia as the first manifestation of antisynthetase syndrome, BMC Med. Notes 9 (290) (2016 June 2) (Epub ahead of print).
[6] J. Morsset, C. Johnson, E. Rich, H. Collard, J. Lee, Management of myositis-related interstitial lung disease, Chest 150 (2016) 1118–1128.
[7] K. Jan, M. Srinaganathan, Acute interstitial pneumonia as first presentation of antisynthetase syndrome: an atypical case, Oxf. Med. Case Rep. 4 (2017) 121–123.
[8] E. Vandenhoute, J. Grutters, J. Aaltenburg, W. Boermans, E. ter Borch, J. van den Bosch, Rituximab in life threatening antisynthetase syndrome, Rheumatol. Int. 29 (2009) 1499–1502.
[9] S. Zampieri, A. Ghirardello, L. Iaccarino, E. Tarricone, P. Gambari, A. Doria, Anti-Jo-1 antibodies, Autoimmunity 38 (2005) 73–78.
[10] S. Toujani, A. Ben Mansour, M. Aki, M. Helhi, J. Cherif, Y. Ouahchy, et al., Acute respiratory failure as the first manifestation of antisynthetase syndrome, Tanaffos 16 (2017) 76–79.
[11] S. Guglielmi, T.M. Mez, M. Gugger, C. Suter, L.P. Nicod, Acute respiratory distress syndrome secondary to antisynthetase syndrome is reversible with tacrolimus, Eur. Respir. J. 31 (2008) 213–217.
[12] M. Qureshi, E. Hoey, T. Fletcher, Z. Ahmed, Antisynthetase syndrome: a case report, Quat. Imag. Med. Surg. 6 (2016) 207–209.
[13] P. Sundaragiri, S. Vallabhasilavu, J. Kanaan, Interstitial lung disease in antisynthetase syndrome without clinical myositis, BMJ Case Rep. (2014), https://doi.org/10.1136/bcr-2014-204926 Apil 3 (Epub ahead of print).
[14] S. Rosa, P. Barreto, M. Mariano, J. Baptista, Inflammatory myopathy and interstitial lung disease in antisynthetase syndrome with PL-7 antibody, BMJ Case Rep. (2014 Oct 7), https://doi.org/10.1136/bcr-2014-204390 (Epub ahead of print).
[15] G. Saito, M. Kono, A. Tsuchumi, Y. Koyanagi, K. Miyashita, T. Kobayashi, et al., Anti-PL-7 antisynthetase syndrome with eosinophilic pleural effusion, Intern. Med. 57 (2018) 2227–2232.
[16] R. Chao, P. Efthimiou, When rheumatology meets pulmonology: antisynthetase syndrome, Chest 152 (2017) A490.
[17] M. Pathria, K. Khan, K. Shah, W. Jhijpratuck, S. Gandhi, G. Krishnaswamy, A variant antisynthetase syndrome: association of eosinophilia, hyperpigmentation, and dust allergy with anti-PL7-mediated multisystemic disease, Chest 152 (2017) A471.
[18] M. Werlang, I. Mira-Avendano, Interstitial lung disease secondary to antisynthetase syndrome presenting as acute respiratory failure, Chest 148 (2015) 404A.
[19] A. Singh, R. Jaiswal, Antisynthetase syndrome - presented as ILD, Chest 145 (2014) 215A.
[20] M. Mortel, P. Ochieng, M. Salvatore, M. Sullivan, Pulse steroids for refractory antisynthetase syndrome: a booster therapy? Chest 148 (2015) 408A.
[21] P. Sundaragiri, S. Vallabhasilavu, J. Kanaan, ILD in antisynthetase syndrome: jo does not muscle his way, Chest 144 (2013) 48A.
[22] E. Murphy, P. Currier, Antisynthetase syndrome presenting as acute respiratory distress syndrome responsive to rituximab, Chest 144 (2013) 434A.
[23] U. Nazir, M. Hamblin, Early use of rituximab for rapidly progressive interstitial lung disease associated with an anti-PL-12 antisynthetase syndrome, Chest 146 (2014) 381A.
[24] C. Kummerfeldt, J. Huggins, E. Riemer, J. Ravenel, T. Whelan, S. Sahn, Pulmonary capillaritis and diffuse alveolar hemorrhage in a patient with moderately positive anti-PL-12 antibodies, Chest 142 (2012) 482A.
[25] A. Rubinowitcz, M. Moon, R. Homer, A 34-year-old man presenting with gradual onset of shortness of breath and interstitial lung disease, Chest 133 (2008) 1041–1047.
[26] M. Merchant, M. Lewis, A 47-year-old woman with worsening dyspnea, arthritis and muscle pain, Chest 142 (2012) 528–531.
[27] B. Hamburg, F. Schneider, M. Woodside, A 48-year-old woman with prior liver disease presenting with dyspnea and ground glass opacities, Chest 141 (2012) 1351–1355.
[28] M. Riveiro-Barciela, A. Labirua-Iturburu, A. Selva-O. Callaghan, A 79-year-old man with dyspnea, dysphagia and weakness, Chest 142 (2012) 252–255.
[29] G. Campos, M. Eisenreich, L. Lopes, R. D'Avila, A. Do Prado, M. Bredemeier, Allergic asthma rescue after acute massive inhalation of wood and paint dust, Scand. J. Rheumatol. 45 (2016) 425–426.
[30] A. Espósito, H. Miot, Syndrome in question: antisynthetase syndrome (Anti-PL-7), An. Bras. Dermatol. 91 (2016) 683–685.
[31] G. Devi, M. Patha, M. Padma, N. Kummadi, Antisynthetase syndrome: a rare cause of ILD. J. Clin. Diagn. Res. 10 (2016) 8–9.
[32] G. Malhotra, N. Ramreddy, S. Chua, M. Iliescu, T. Kaur, A curious case of acute respiratory failure: is it antisynthetase syndrome? Case Rep. Crit. Care (2016 June 28), https://doi.org/10.1155/2016/7379829 (Epub ahead of print).