CASE REPORT

Refractory polymyositis undergoing remission following antitubercular therapy

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SUMMARY

Opportunistic infections pose a significant problem in patients receiving immunosuppressive therapy for autoimmune diseases. We present a case of a woman with polymyositis refractory to high-dose steroid and methotrexate, as a consequence of which she developed miliary tuberculosis. Her myositis went into remission after initiation of antitubercular therapy, in spite of bringing down the intensity of immunosuppression. This is the first reported case of myositis undergoing remission after treating intercurrent infection, and illustrates the complex relationship between autoimmune disease and host response to infection.

BACKGROUND

Infections pose a significant challenge during treatment of autoimmune diseases. We present a patient with refractory polymyositis who developed miliary tuberculosis on immunosuppression and unexpectedly achieved remission after antitubercular therapy (ATT). This case highlights the intriguing inter-relationship between autoimmunity and infection.

CASE PRESENTATION

A 52-year-old postmenopausal woman presented with predominant proximal muscle weakness in extremities, neck and trunk for 2 months, which was disabling to the extent she was completely restricted to bed. She had no fever, weight loss, skin rash, joint pains, oral ulcers, photosensitivity or alopecia. Comorbidities included hypertension (for which she was on telmisartan 80 mg hydrochlorothiazide 12.5 mg once daily) for the past 4 years and hypothyroidism (diagnosed 2 months earlier and for which she was on levothyroxine 100 µg/day). Examination confirmed proximal limb, neck and trunk weakness ([figure 1](#)) without pharyngeal or respiratory muscle involvement. Systemic examination was otherwise unremarkable.

INVESTIGATIONS

Investigations revealed elevated muscle enzymes (creatinine phosphokinase 4409, lactate dehydrogenase (LDH) 2069, aspartate aminotransferase 321, alanine aminotransferase 323 (units IU/L for all); [figure 1](#)). Electromyogram was consistent with inflammatory myositis. A screen for malignancy (breast, gynaecological and otorhinolaryngological examination, chest X-ray, ultrasound of the abdomen and mammography) was negative. Muscle biopsy, although ideal, was not feasible due to lack of patient consent.

DIFFERENTIAL DIAGNOSIS

In view of predominant proximal muscle weakness with elevated muscle enzymes and a myopathic pattern on electromyogram, probable polymyositis (as per the Bohan and Peter¹ criteria) was the best-fit diagnosis. In view of the patient's age, malignancy-associated myositis was also considered in the differential diagnosis; however, the malignancy screen as aforementioned was negative.

TREATMENT

The patient was started on prednisolone 60 mg/day, and oral methotrexate, weekly instituted, was added a month later (gradually increasing to 25 mg/week). She developed steroid-induced diabetes treated with metformin and insulin. In spite of immunosuppression, her muscle weakness had shown only partial improvement ([figure 1](#)) by the sixth month of therapy, with inability to taper prednisolone below 50 mg/day; hence, she was planned for rituximab as second-line immunosuppression since she was refractory to high-dose steroids and methotrexate in combination. Eight months after the first visit, she presented with 10 days of intermittent fever (up to 103°F) along with cellulitis at the base of the right little finger. She continued to have proximal limb and neck weakness ([figure 1](#)); systemic examination was otherwise unremarkable. Hand X-ray showed no underlying osteomyelitis ([figure 2](#)). She was treated with injectable amoxycillin-clavulanate, with oral clindamycin added after 5 days. The steroid dose was halved, and methotrexate stopped due to intercurrent infection. The area of cellulitis ulcerated; cultures from the site as well as blood cultures were negative. Non-resolution of fever and cellulitis by 1 week mandated a search for alternate causes. Chest radiograph showed miliary shadows in bilateral lung fields ([figure 3](#)); a CT of the chest showed miliary shadows in both lung fields with necrotic mediastinal lymph nodes ([figure 4A, B](#)). Tuberculin skin test and interferon γ release assay were negative. Since cell-mediated immune responses could be anergic in the context of miliary tuberculosis as well as due to steroid therapy,² tuberculosis was still considered most likely in our scenario. The patient was started on four-drug ATT with isoniazid, rifampicin, pyrazinamide and ethambutol, with rituximab planned for the myositis after completing the intensive phase (due to its B-lymphocyte selective action, it remains an option for patients with tuberculosis, where T lymphocytes play a predominant role in host immune response. It has been used in patients with rheumatoid arthritis having

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Figure 1 Summary of clinical course. *Power graded as per Medical Research Council Grading with a maximum of 5. **LES—patient developed ATT-induced transaminitis—AST/ALT 151/229 from 36/80 3 weeks prior—necessitating change to modified ATT with levofloxacin, ethambutol and streptomycin daily regimen. CPK, creatine phosphokinase (IU/L); LE, levofloxacin and ethambutol; LDH, lactate dehydrogenase (IU/L); Pred, prednisolone daily dose (mg); MTX, methotrexate weekly dose (mg); ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATT, antitubercular therapy; HRZE, isoniazid, rifampicin, pyrazinamide and ethambutol daily regimen.

reactivation of tubercular infection after use of antitumour necrosis factor agents. However, it is often felt prudent to avoid introducing any biological agent in patients with active tuberculosis, unless the intensive phase of ATT has been completed, hence the decision to first complete the intensive phase of ATT and then institute rituximab therapy.^{3 4} Although her fever remitted, the patient developed transaminitis on ATT, which necessitated change to levofloxacin, ethambutol and streptomycin from the second month onwards, followed by levofloxacin and ethambutol from the fifth month for maintenance. By the time the intensive phase of ATT was completed, her proximal muscle weakness had markedly improved. She did not require the previously considered therapy with rituximab for control of myositis.

OUTCOME AND FOLLOW-UP

Subsequently, the patient achieved full remission of myositis at completion of 9 months of ATT, on prednisolone 12.5 mg/day.

Figure 2 X-ray of hands showing increased soft tissue shadow at the base of right little finger (white arrowhead).

Methotrexate was restarted orally for maintenance at a dose of 10 mg/week (increasing to 20 mg at the last follow-up), and prednisolone was further reduced (to 10 mg daily at the last visit). Two months after completing the course of ATT, she continued to be in remission on the aforementioned doses of prednisolone and methotrexate. Her steroid-induced diabetes had also resolved.

DISCUSSION

Our patient had a clinical diagnosis of polymyositis (proximal weakness with elevation of muscle enzymes and electromyogram consistent with inflammatory myositis). She had only partial remission of muscle weakness in spite of being on standard immunosuppressive therapy for 9 months. Owing to immunosuppression, she developed tuberculosis, which remains a major concern in countries such as India where mycobacterial

Figure 3 Chest X-ray in October 2013 showing miliary shadows in both lung fields.

Figure 4 (A and B) CT of the chest showing miliary shadows in both lung fields.

infection is endemic,^{5–7} and steroid-induced diabetes further predisposed her to develop this event. It is challenging to explain why her myositis went into remission after starting ATT.

Increase in type I interferons in peripheral blood leucocytes has been observed in response to mycobacterial infection in vivo. Peripheral blood monocytes from patients with active, but not latent tuberculosis, increases production of type I interferons on stimulation, suggesting a relationship of type I interferons with active tuberculosis infection. By its differing actions on different cell types, type I interferons are protective as well as harmful in tuberculosis. They promote immunogenicity of BCG vaccine by stimulating dendritic cells. At the same time, interferon β also leads to abnormal IL-1 β production in macrophages resulting in decreased clearance of intracellular mycobacterial infection.⁸ Unlike tuberculosis, the aetiology of idiopathic inflammatory myositis (IIM) is unknown. However, in patients with established IIM (polymyositis and dermatomyositis), a type I interferon signature has been demonstrated in peripheral blood as well as in muscle biopsies, and this has been found to decrease on attaining remission.⁹ Activated lymphocytes producing interferon are likely responsible for driving the pathology of IIM. Anti-interferon α therapy (sifalimumab) in a recent phase 1b study has shown promising results with neutralisation of type I interferon signature in muscle biopsies of patients with polymyositis and dermatomyositis, and this has correlated with improvement in manual muscle testing.¹⁰ It is possible that the mycobacterial infection might have led to increased levels of

interferon α and hence contributed to the refractoriness of myositis to therapy with steroid and methotrexate. Hence we hypothesise that a reduction in the type I interferon level in response to therapy for mycobacterial infection could have aided in resolution of the previously difficult-to-treat polymyositis in our patient. Unfortunately, we have not tested levels of type I interferon in the peripheral blood of our patient, which could have confirmed our hypothesis.

Tuberculosis is also associated with increased circulating IL-17 and IL-10 (the latter enables persistence of intracellular mycobacteria by inducing regulatory T lymphocytes specific to mycobacterial antigen).¹¹ Muscle biopsies in polymyositis show increased IL-17 and IL-10 mRNA;⁹ so it is reasonable to hypothesise that normalisation of these cytokines with ATT may have helped in improvement of myositis.

Delayed response to immunosuppression as a cause for remission was unlikely, as the steroid dose was halved and methotrexate stopped at the time of diagnosis of miliary tuberculosis. Previous attempts to reduce the daily steroid dose below 50 mg prednisolone had led to worsening of muscle weakness, hence steroid-induced myopathy was not a plausible alternative explanation. Persistent elevation of muscle enzyme (LDH) was also not consistent with the condition. The patient also had no clinical or laboratory features of thyrotoxicosis or hypothyroidism that could have adversely affected muscle power; moreover, she was on a constant dose of levothyroxine (100 μ g daily) from the time she was diagnosed with polymyositis up until the last follow-up visit.

Reports exist of autoimmune disease remitting after treatment of opportunistic infection.¹² To the best of our knowledge, this is the first report of inflammatory myositis resistant to standard immunosuppressive therapy remitting after treatment of supervening miliary tuberculosis. This case emphasises the complex interplay of autoimmunity and infection.

Learning points

- Opportunistic infections such as tuberculosis pose a significant problem in patients receiving immunosuppressive drugs.
- A simple chest radiograph can aid diagnosis in patients with no other obvious cause of fever.
- A complex interplay exists between infection and autoimmunity, and similar mechanisms may drive disease in both of these settings.

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