CASE REPORT

Polymyalgia rheumatica development in a patient under PI3K inhibitor therapy for chronic lymphocytic leukaemia

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SUMMARY

We report a patient with chronic lymphocytic leukaemia (CLL) who was treated with idelalisib, a PI3K δ inhibitor with rituximab. After 20 weeks of treatment, the patient developed classical signs and symptoms of polymyalgia rheumatica (PMR) in association with an elevated C reactive protein of 74 mg/L. After 2 weeks of prednisolone 15 mg daily symptoms had resolved and acute phase markers normalised. To our knowledge, this is the first report of PMR developing as a complication of PI3K δ inhibitor treatment of CLL.

BACKGROUND

Polymyalgia rheumatica (PMR) is a common inflammatory condition affecting patients older than 50 years.^{1,2} The classical presentation is with pain and stiffness of the neck, shoulder girdle and hip girdle in association with elevated inflammatory markers.^{1,2} The diagnosis remains clinical and the pathogenesis remains unknown. It is typically treated with 12.5–25 mg oral prednisolone.² There is a clinical overlap with the related condition giant cell arteritis (GCA)¹; both conditions are associated with elevated circulating interleukin (IL)-6 levels. Here, we report a case of chronic lymphocytic leukaemia (CLL) that developed PMR following therapy with idelalisib, a PI3K δ inhibitor, and rituximab.

CASE PRESENTATION

An 85-year-old Caucasian woman received idelalisib (Zydelig, Gilead Sciences) together with rituximab as part of a clinical trial for patients with previously untreated CLL with chromosome 17p deletion.

The patient had been diagnosed with CLL in January 2013, initially presenting with anaemia, recurrent disseminated herpes zoster and a severe chest infection, without B symptoms. At first, she was managed conservatively. However, over the next 2 years, her CLL progressed, with anaemia, thrombocytopenia, lymphocytosis, widespread lymphadenopathy and palpable hepatosplenomegaly.

In 2015, she commenced a clinical trial (Gilead GS-US-312-0133; EudraCT no: 2013-003314-41) in which rituximab 375 mg was administered intravenously once weekly for 8 weeks with oral idelalisib 150 mg given twice daily continuously throughout the study. Prior to treatment, her haemoglobin (Hb) was 7.5 g/dL, white cell count

(WCC) $163 \times 10^9/L$, lymphocytes $160 \times 10^9/L$, platelets $54 \times 10^9/L$ and lactate dehydrogenase (LDH) 777 IU/L (normal range 70–250 IU/L) and her C reactive protein (CRP) was 15.5 mg/L. Anti-nuclear antibody was negative, plasma viscosity of 1.85 mPa-s, IgM 0.66 g/L, IgA 0.18 g/L and IgG 8.8 g/L. Serum protein electrophoresis revealed an IgG kappa paraprotein.

After 10 weeks of treatment within the clinical trial, she complained of 'bone pains' that she managed with simple analgesia. After 18 weeks of therapy with idelalisib, she presented with increasing pain in her neck, shoulders and thigh muscles, early morning stiffness lasting greater than 1 hour and difficulty getting out of bed. Examination revealed limitation of movement of upper and lower limbs and clinical features suggestive of bilateral subacromial bursitis. There was no clinical evidence of synovitis, myositis or neurological disease.

INVESTIGATIONS

Blood tests revealed normal creatine kinase and an elevated CRP at 45 mg/L. Autoantibodies including antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) and rheumatoid factor were negative. Immunoglobulin levels had remained low since commencing the trial. Complement levels were normal.

DIFFERENTIAL DIAGNOSIS

Our patient had classical signs and symptoms of PMR; however, clinical challenges exist in distinguishing PMR from other disease mimics, including GCA, infection, malignancy, endocrine disorders and elderly onset rheumatoid arthritis. The most commonly misdiagnosed diseases include malignancy and rheumatoid arthritis.³ Relevant tests that help to exclude PMR disease mimics include a negative rheumatoid factor, anticyclic citrullinated peptide antibody, ANA, together with normal levels of thyroid-stimulating hormone, creatine kinase, serum protein electrophoresis and vitamin D.

TREATMENT

She was initially treated with 2 weeks of 10 mg prednisolone with no symptomatic response and a rise in her CRP to 74 mg/L. The dose of oral prednisolone was therefore increased to 15 mg daily, together with injection of 40 mg methylprednisolone

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(Depo-Medrone) to the subacromial bursa on each side. This resulted in complete resolution of her pain within 3 weeks and a fall in CRP to 5.7 mg/L. This pattern of response to the said dose of glucocorticoid is very characteristic of PMR.

OUTCOME AND FOLLOW-UP

She followed a prednisolone taper following American College of Rheumatology/European League Against Rheumatism guidelines. Three months from her original presentation, after reducing the prednisolone dose from 10 to 9 mg, she had a relapse of symptoms in association with a rise in CRP to 39 mg/L. This responded well to an increase in prednisolone dose to 10 mg daily.

Throughout the above, the patient continued to take idelalisib 150 mg twice a day. Her underlying haematological disease responded extremely well with improvement in her blood indices (Hb 9.8 g/dL, WCC of $5.17 \times 10^9/L$, lymphocytes $2.05 \times 10^9/L$, platelets $136 \times 10^9/L$, LDH 559 IU/L) and CT scans showing significant reduction in nodal disease.

DISCUSSION

Idelalisib is a first-in-class inhibitor of phosphatidylinositol-3-kinase (PI3K) p110 isoform δ .⁴ PI3K δ is highly active in B cell malignancies and plays an essential role in the B cell receptor pathway signalling and regulates cell proliferation, increased cellular metabolism and resistance to apoptosis.^{4,5}

Idelalisib is used in combination with rituximab as a treatment option for patients with relapsed CLL, has shown an overall response rate of 81% and overall survival of 91% at 12 months.⁶ In October 2015, it was approved by National Institute for Health and Care Excellence for patients with untreated CLL with a chromosome 17p deletion or tumour protein p53 mutation or those with relapsing CLL treated less than 24 months previously.⁷ The p53 gene is located to the most distal band on the short arm of chromosome 17 (17p13).⁸

Although immunologically mediated events such as enterocolitis,^{9–11} glucocorticoid-responsive hepatitis¹² and pneumonitis are well-recognised complications of idelalisib therapy, this is the first report of this agent being linked to PMR. There are also no reports to our knowledge of PMR development following rituximab therapy.

The question arises whether rituximab, which works to deplete B cells, contributed to the pathogenesis of PMR. Rituximab has been widely used in autoantibody-associated diseases where to our knowledge it is not associated with development of PMR-like or GCA-like syndromes. Furthermore, there has been a reported case of successful use of rituximab in the treatment of GCA.¹³

There is also evidence of disturbed homeostasis of B cells in patients with newly diagnosed GCA or PMR¹⁴: patients had decreased numbers of B cells compared with patients with untreated rheumatoid arthritis and healthy controls.¹⁴ Following glucocorticoid-induced remission, the number of B cells normalised and exhibited an enhanced IL-6 response.¹⁴ This research helps to add to the discussion of the underlying pathogenesis of PMR.

There are reports of PMR occurring in association with haematological malignancies including CLL.^{15–19} Therefore, a role for the underlying haematological disease in the development of PMR cannot be ruled out. It is also plausible that in this case, the mechanism involved a disease–treatment or treatment–treatment interaction.

PMR has been reported to occur in patients receiving immunosuppression, for example, a case of a patient on triple therapy (tacrolimus, mycophenolate mofetil and prednisone) for renal transplant.²⁰ Two patients were reported to develop PMR/GCA after treatment with ipilimumab, an antagonist of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) that has immune-potentiating effects.²¹ An agent with the opposite function, CTLA-4-Ig, has reportedly shown intriguing results in early trials for GCA.²²

PI3K inhibition affects many cell lineages in the immune system.^{4,5} There is some controversy regarding its effect on regulatory T cells (Tregs)^{23,24} which normally function to control autoimmunity and inflammation via local action of cytokines such as IL-10, transforming growth factor- β and IL-35 which modulate the function of lymphocytes and antigen-presenting cells.²⁴ In a mouse model, chronic PI3K inhibition led to the development of colitis and Sjogren's syndrome via suppression of Treg cell function.²⁴ Inhibition of Tregs has previously been demonstrated with PI3K-Akt pathway inhibitors.²⁵ These resulted in a significant and selective reduction in Tregs in vivo, both in naive and tumour-bearing mice; additionally, the significant antitumour effect observed was shown to be Treg dependent.²⁵

Research focusing on T cell subsets and their role in PMR pathogenesis shows varied results. Previous research suggests a possible relationship between ageing of regulatory T cells and an increased risk of autoimmunity, cancer and infections in the elderly, however the exact mechanisms underlying this process remain unclear.²⁶ It has been reported that premature ageing of effector memory and terminally differentiated CD8+ T together with increased proinflammatory potential of CD8+ T cell has a role in PMR pathogenesis.²⁷ However, no obvious changes in Th-subsets and regulatory T cells were observed in these patients.²⁷ Interestingly, research investigating the role of major CD4+ T cell subsets has shown that patients with untreated GCA/PMR had decreased frequency of Treg cells and Th1 cells, but a significantly increased percentage of Th17 cells when compared with healthy controls.²⁸

Recent studies have shown that immune checkpoint inhibitors which are immunostimulatory in nature are associated with PMR development which was reported in four cases and where PMR responded to standard therapy.²⁹ Off note, the most severe toxicity in the checkpoint inhibitor class of drugs including anti-CTLA-4 and anti-programmed cell death protein 1 (PD-1) and anti-PD-L1 is gut toxicity and this is more common with anti-CTLA-4.³⁰ A key mechanism of action of anti-CTLA-4 is thought to be inhibition of regulatory T cells.³¹ Idelalisib is viewed as predominantly immunosuppressive due to its depletion of immune cells including lymphocytes. The most common severe toxicity with idelalisib is also gastrointestinal toxicity, with diarrhoea occurring in 47% and fatal and/or serious colitis occurring in 14%–19%.^{9–11} The apparent association of both checkpoint inhibitors and idelalisib with PMR might be the common denominator that both classes of drug cause immune dysregulation and disrupt regulatory T cell function.

Several studies have demonstrated the important role of IL-6 in the pathogenesis of PMR and its role in Th17 cell survival and development. A recent review of the literature shows promising options for the future.³² Here, tocilizumab used either with prednisolone or alone appeared effective and safe in treating patients with PMR.³² Further supporting evidence of anti-IL-6 therapy for PMR may come from an ongoing prospective, open-label, phase IIa trial of tocilizumab.³³

Learning points

- Polymyalgia rheumatica (PMR) is a very unusual complication of immunosuppression but one of which prescribing clinicians should be aware as it can cause distressing symptoms that are treatable with the correct dose of oral glucocorticoid therapy.
- We suggest that, at least in this case, the mechanism might be related to a reduction in regulatory T cell function.
- This is particularly interesting given recent reports of a hypoproliferating regulatory T cell compartment with impaired function in active giant cell arteritis; in this study, tocilizumab appeared to restore regulatory T cell numbers and activation markers.³⁴
- We suggest that the potential role of circulating regulatory T cells in PMR, and its relationship to interleukin-6, requires further investigation.

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