CASE REPORT

Resistant type II cryoglobulinaemic vasculitis successfully treated with bortezomib in a patient with SLE

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SUMMARY

We report an interesting case of hepatitis C virus-negative type II cryoglobulinaemic vasculitis (CV) in a patient with a background history of systemic lupus erythematosus. The type II CV became less responsive to traditional treatments over time and culminated in an intensive care unit admission with critical multiorgan failure. A detailed flow cytometric evaluation of the bone marrow proved to be helpful in treatment. It demonstrated that bortezomib was a viable alternative treatment option for the type II CV. The patient received bortezomib and has made a full and durable recovery.

BACKGROUND

The two messages of our paper are first, an inhibition of the proteasome, by bortezomib, which targets plasma cells rather than CD20-positive lymphocytes, may be an option in the case of lupus-associated cryoglobulinaemic vasculitis (CV); and, second, that a deeper flow cytometric analysis of the bone marrow may drive the treatment strategy in refractory cases of CV.

CASE PRESENTATION

We report the case of a 49-year-old woman with hepatitis C virus-negative type II CV on a background of systemic lupus erythematosus (SLE). The patient had met the 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus based on positive antinuclear antibodies, low C4, leukopaenia, lymphopaenia, acute cutaneous lupus erythematosus and arthralgia several years prior. The diagnosis was

supported by the positive anti-Ro-52/60 antibody and Raynaud's phenomenon. Protein electrophoresis at the time of SLE diagnosis was normal. After 3 years of stable SLE control, the patient suddenly showed features of type II CV. Clinical features of type II CV were recurrent cutaneous purpura and ulceration of the legs complicated by secondary infection. Nephritis was not present but she had neuropathic pain of the feet for many years. Her treatment history involved four cycles of rituximab (RTX) and a single course of intravenous cyclophosphamide (CYC). All of these therapies were ineffective. Despite the resistant disease, immunoglobulin (Ig)M-kappa and IgG-kappa paraproteins were detectable but unquantifiable. Total IgM level was 2.06 g/L (0.50–2.00), IgG 1.7 (6.0–16.0), RF 21 (<15), C4 <0.02 (0.14–0.54) and C3 <0.62 (0.75–1.65). Serum-free κ -light chains (κ -LC) were 49.9 (6.7–22.4), λ -light chains (λ -LC) 16.2 (8.3–27.0) and κ/λ ratio was 3.080 (0.310–1.560). Cryoprecipitate immunofixation showed an IgM- κ , small IgG- κ and small IgA- λ band. Naïve B cells were detectable at $0.002 \times 10^9/L$ and memory B cells at $0.0007 \times 10^9/L$. Repeat bone marrow analysis was performed and showed a small plasma cell population that had immunophenotypic characteristics of myeloma plasma cells (0.23% of leucocytes of which 20% had a neoplastic phenotype CD19-CD56+C-D27+(weak)CD45+(weak)). A skin biopsy was not sought because the clinical appearance of the rash was typical for leucocytoclastic vasculitis and the serological findings, which were classical for type II CV vasculitis, were felt to be more useful than skin histology in establishing the aetiology.

Figure 1 Cutaneous features before and after bortezomib. (A) Purpuric rash and (B) leg ulceration before bortezomib treatment. (C) and (D) Resolution of these features 19 months after bortezomib.

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In view of these findings, treatment strategy was switched from immunosuppression to targeting antibody and plasma cells. She was given three exchanges of PEX and three doses of intravenous methylprednisolone. The IgM band disappeared but a detectable unquantifiable IgG- κ paraprotein remained. After the first PEX, the response was good: her cutaneous disease and peripheral neurology remitted then returned after 6 months. However, on repeated PEX, the purpuric rash on her legs returned after only 5 weeks. Repeat laboratory assessment showed κ -LC elevated at 33.2mg/L, λ -LC 15.3 and κ/λ ratio 2.170. Repeat bone marrow trephine detected an increase in the population of aberrant plasma cell since the last biopsy (0.8% of leucocytes of which 67% had a neoplastic phenotype CD19-CD56+CD27++(weak)CD45-).

A chemotherapeutic tactic usually reserved for multiple myeloma, bortezomib, was considered but funding was declined given the absence of internal organ involvement and the low level of bone marrow plasma cell dyscrasia seen. However, during her follow-up, she experienced a severe CV relapse with widespread ulcerative purpura, acute renal failure, pulmonary vasculitis and fevers leading to intensive care unit admission. The estimated glomerular filtration rate was 27 mL/h (from >90 mL/h); urinary red cell count 3048/hpf; urinary white cell count 205/hpf; urinary protein to creatinine ratio 243 mg; C4 <0.04 and C3 0.58. High-resolution CT of the chest showed bilateral pleural effusions and adjacent lung consolidation.

INVESTIGATIONS

See above

TREATMENT

She was then treated with six cycles of PEX then bortezomib 1.3 mg/m² intravenously combined with 2 days of 20mg dexamethasone on days 1, 4, 8 and 11 repeated every 21 days for a total of four cycles. Weekly CYC PO 500mg was given for 3 weeks as an adjunctive agent, as per protocol in treatment regimens for multiple myeloma; however, the CYC was not felt to be a durable agent in her response given her previous non-response to the drug.

Following this, there was the rapid and progressive resolution of the vasculitic rash (figure 1) and other CV features, with the disappearance of the IgG paraprotein and aberrant κ/λ ratio. This was consistent with the expected mechanism of action of bortezomib in eliminating the pathogenic plasma cell clones. Clinical regression of CV features in the patient eliminated the need for a repeat bone marrow assessment. The patient reported a subjective improvement and now only a mild painful peripheral neuropathy remains. Her bortezomib course was complicated by a single episode of infectious gastroenteritis requiring intravenous hydration and oral antibiotics. No new events of peripheral neuropathy occurred. Transient post-infusion fatigue occurred during each visit.

OUTCOME AND FOLLOW-UP

Nineteen months later, the patient remains in clinical remission on prednisolone 4mg/day and hydroxychloroquine 200mg/day. The CV features have not recurred and we have not observed lupus activity. Her latest serum immunofixation, immunoglobulin, κ/λ ratios and complement levels have been within normal limits. She continues on a surveillance programme with 4-monthly paraprotein measures and 3-yearly bone marrow biopsies.

DISCUSSION

A B-cell targeted strategy is usually justified in type II CV as the cryoglobulins are traditionally IgM paraproteins associated with small clonal B-cell populations in the marrow. Our case

was unusual in that the type II CV was driven by a small clonal plasma cell population that lacked CD20 and had immunophenotypic characteristics of myeloma plasma cells. This explained the failure to respond to anti-CD20 therapy (RTX) because most plasma cells lacked CD20 or expressed it weakly.¹ Although this patient did not meet International Myeloma Working Group criteria for multiple myeloma based on blood and urine electrophoresis or size of the bone marrow plasma cell population, bortezomib, a proteasome inhibitor, proved the ideal alternative due to its direct apoptotic and antiangiogenic effects on the aberrant plasma cells.²

Our case demonstrates the value of detailed flow cytometric evaluation of the bone marrow of refractory patients with type II CV. The value lies in identifying the driving clonal cell population (whether it be clonal B cells or plasma cells) and the presence or absence of the CD20 cell surface protein (which is a prerequisite for response to RTX). This strategy of therapeutic planning is in lieu of therapeutic selection according to the subtype of paraprotein. RTX is often publicised to be a first-line therapeutic option in IgM-associated CV.^{3,4} However, as we have described, response to RTX therapy is determined not by the paraprotein expressed, but rather by the underlying aberrant clonal cell.

There is now an increasingly recognised range of paraprotein-related syndromes in which the features relate to the physicochemical or immunological properties of the paraprotein and aberrant clonal cell population rather than disease bulk. We believe that the dominant clone(s) arose in our case from a pool of polyclonal autoreactive B cells due to chronic SLE. Individuals with autoimmune rheumatic disease are known to share an increased risk of developing malignant haematological disease. There are several case reports of successful use of bortezomib in type I CV and a case series in SLE without cryoglobulinaemia; however, this is the first known case report for its successful use in type II CV.⁵⁻⁹

Patient's perspective

It is 2 years on 16 October 2018 that I had my last treatment of bortezomib. At that time I was taking 30mg of prednisolone per day. Since the treatment, I have now been able to reduce my steroid intake to 0.5 mg per day and I am hoping to be able to stop taking this medication altogether in the very near future. Everything is working out so well. There is no sign of the rash or ulcerations and I am feeling really well. Everything is working as it should!

I would also like to add that having the treatment and the results that have been achieved have been life changing for me and my family. To now be happy and feeling positive about myself and our future, is worth everything to us and without the treatment this would not have been possible. Prior to this treatment we thought we had reached the end and that nothing more could be done. It really has been life changing for us. .

Learning points

- There are now an increasingly recognised range of paraprotein-related syndromes.
- Bone marrow biopsy may be useful in refractory cases of hepatitis C virus-negative type II cryoglobulinaemia to delineate the cause and guide treatment.
- Bortezomib may be better than rituximab in some type II cryoglobulinaemia cases.

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