CASE REPORT

Postsurgical pyoderma gangrenosum after an autologous stem cell transplantation for multiple myeloma

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SUMMARY

We report a man who underwent autologous stem cell transplantation (ASCT) for multiple myeloma. Two months after ASCT, he presented with necrotising cholecystitis due to gallbladder stones and was submitted to laparoscopic cholecystectomy. About a week later, he developed progressive skin ulcers at sites where trochanters had been inserted. Progressive enlargement and necrotic aspect of these ulcers took place despite debridement and large spectrum antibiotics. New ulcers developed at the site of enoxaparin injection at the right arm (pathergy phenomenon). A skin biopsy and clinical evaluation favoured the diagnosis of pyoderma gangrenosum (PG). He was treated with daily methylprednisolone and dapson with improvement of the lesions. This is the first case in the literature of PG after ASCT. Despite the risk factors, the onset of an autoinflammatory disease right after the transplant is intriguing since PG is extremely rare in immunocompromised patients.

BACKGROUND

Pyoderma gangrenosum (PG) is a rare inflammatory neutrophilic dermatosis, with multiple clinical presentations, including pustules, abscesses, papules, nodules, plaques and ulcers and has recently been included within the spectrum of autoinflammatory diseases. Its pathogenesis is elusive, but upregulation of neutrophilic function and secondary release of cytokines are proposed to drive the process.¹⁻⁴ Operative trauma and pathergy, likely through upregulation of neutrophils function, seem to be additional risk factors for postsurgical PG (PSPG).¹ The treatment landmark is long-term immunosuppression.² We present a case of PG onset after autologous stem cell transplantation (ASCT) for multiple myeloma (MM) in a patient who had also recently been submitted to abdominal surgery. As far as we know, it has never been described short term after ASCT.

CASE PRESENTATION

A 51-year-old Caucasian man was diagnosed with MM in 2014. He received six cycles of bortezomib, cyclophosphamide and dexamethasone. After initial treatment, he achieved very good partial response (VGPR) and underwent high-dose melphalan

(200 mg/m²) followed by ASCT, in October 2015; time to neutrophil engraftment was 11 days. He had no significant medical history aside from MM and congenital solitary kidney. His family history was positive for both his mother and brother having had gastric cancer.

Two months after ASCT, he presented with the onset of a fever (38.2°C) and abdominal pain. He was admitted for investigation, diagnosed with acute cholecystitis and was submitted to laparoscopic cholecystectomy which confirmed an acute necrotic cholecystitis (figure 1). No immediate complications were observed right after surgery, and hospital discharge took place 3 days later. However, about a week after the procedure, he was readmitted with fever and skin lesions, nausea, hyporexia and mild abdominal pain. The skin lesions were two warm, hyperaemic and indurated ulcers on his abdomen. The ulcer base was necrotic and filled with brownish purulent discharge (figure 2). The skin surrounding the wounds was indurated and erythematous. The lesions were at sites corresponding to where trochanters had been inserted for the laparoscopy. One was 10 cm wide and located in the epigastric region; the other was 4 cm wide and was periumbilical. It was noted that he had an equimotic and indurated subcutaneous lesion on the right arm, originally acquired from a heparin shot during his previous admission; within a few days, it developed a central ulceration. Considering the possibility of surgical site infection, he was started on antibiotic therapy, but evolved with septic shock and needed to be transferred to an intensive care unit. The general surgery team re-explored his abdomen and performed a deep wide debridement from the skin to the aponeurosis, from the subxiphoid to the umbilical region. The dermatology team was contacted to evaluate the skin lesions, and a skin biopsy of the right arm was obtained (figure 3).

INVESTIGATIONS

MM assessment prior to ASCT attested VGPR.⁵ Only IgG/kappa paraprotein remained detectable by serum immunofixation. Six months after ASCT, it was undetectable. At this time point, reevaluation also showed that, although his lymphocyte count was normal (1.290/mm³) polyclonal IgG levels after ASCT were still low (357 mg/dL—laboratory reference: 952 mg/dL), suggesting immune paresis

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Figure 1 Timeline showing the main events.

after ASCT. Abdominal CT performed at readmission showed fluid and densification in areas of the ulcers, but due to acute renal dysfunction, no contrast was used compromising accuracy for diagnosis of intra-abdominal fluid collection. A second abdominal CT this time with intravenous contrast, 10 days later, showed no fluid collection. No bacterial infections were identified; however, while hospitalised for the ASCT, he was colonised by *Klebsiella pneumoniae* carbapenemase (KPC), which was later also found at the culture of the biopsy of the right arm skin. Immunohistochemical analysis, however, favoured the diagnosis of PG, which was in accordance with the clinical evaluation and the specialist's opinion. Inflammatory response was supported by high levels of C reactive protein, achieving a maximum of 386.5 mg/L (laboratory reference <5.0 mg/L), at the time of diagnosis with a descent reduction to normal levels of 1.0 mg/L after treatment. His white cell count was also elevated at diagnosis, $30.8 \times 10^9/L$ (neutrophils of $28.1 \times 10^9/L$), and decreased after treatment to normal levels of $5.4 \times 10^9/L$ (neutrophils of $4.3 \times 10^9/L$). Rheumatoid factor, anticitrullinated protein antibodies, antinuclear antibody titre and antineutrophil antibody titre were all tested negative, distinguishing its cause from collagen disease or vasculitis.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of PG is wide, including infections, malignancies, vascular diseases, systemic conditions specially Sweet's syndrome (SS).⁶ In our case, the previous surgical manipulation, and presentation compatible with PSPG, led to confusion with surgical site infection. Early clinical signs and symptoms of PSPG are erythema developing after surgery around suture lines or the incision itself.² Subsequently, the wound may form small areas of

discharge with punctate ulcerations, which coalesce into larger areas of wound dehiscence. There seems to be an anatomic predilection of PSPG for the breast and abdomen.² Due to the rarity of PSPG compared with wound infections, antibiotic drug therapy is often initiated, and debridement of the wound is performed because of the devastating deaths associated with necrotising fasciitis. Diagnosis of PSPG is difficult even when clinical suspicion is present. It is a diagnosis of exclusion, with negative cultures, clinical presentation, suggestive histology, pathology and even response to immunosuppressive therapy.² Biopsies show no specific diagnostic features; in many cases, they can help exclude other conditions such as malignancy, infection or cutaneous vasculitis.⁵ Delay in diagnosis and inappropriate treatment can be devastating to the patient with PG.

TREATMENT

Our patient was initially treated with antibiotics (vancomycin, colistin and tigecycline) considering the KPC colonisation and the patient's clinical deterioration. After the biopsy, he was started on daily methylprednisolone (80 mg) and dapsone (100 mg), with improvement of the skin lesions. Due to pathology, any other invasive approach, such as surgical manipulation or debridement, was contraindicated. Plastic surgery and stomatology teams provided orientation on local care of the wounds.

Currently, there are no guidelines to the management of PG. Most systemic treatments include steroids and immunosuppressive drugs.⁷ Corticosteroid-sparing agents, topical therapy and hyperbaric oxygen have been reported less commonly.² Recently, good response has been reported for treatments based on anti-tumour necrosis factor alpha, and infliximab proved effective in a randomised controlled trial.⁷ Most investigators recommend avoiding surgery because of the potential for additional

Figure 2 Epigastric lesion showing purulent discharge and perilesional erythema.

Figure 3 The image of skin fragment shows epidermis with spongiosis and presence of rare polymorphonuclear leucocytes. There are segments with dermal-epidermal detachment, and presence of inflammatory exudate of the blood vessels, hair follicles and sudoriferous glands. The histopathology is suggestive of pyoderma gangrenosum.

pathergy. Median time to lesions resolution is 4.2 months and may vary depending on the area of involvement and mainly time to diagnosis to therapy.²

OUTCOME AND FOLLOW-UP

The patient was discharged in February 2016. Skin lesions had already shown important signs of improvement. He was receiving dapsone and gradual dose reduction of oral prednisone. In April 2016, he had his last appointment with the bone marrow transplantation team. He showed marked recovery, had regained some independence of his daily activities and had no pain, infection or signs of MM. At this time, he was sent back to the primary haematology centre where he was seen with priority for further follow-up regarding MM, and continued follow-up with the dermatology, plastic surgery and stomatherapy teams. We learned from his family that he had died from an infection 6 months later.

DISCUSSION

PG may precede, coexist with or follow different systemic diseases, notably inflammatory bowel diseases, haematological malignancies and rheumatic disorders or it can be idiopathic.¹² It may also occur in the context of classic syndromes like pyogenic arthritis, yoderma gangrenosum and acne; synovitis, acne, pustulosis, hyperostosis and osteitis); and the recently described PG, acne and suppurative hidradenitis.¹⁸ Various non-specific cutaneous manifestations have been described in association with MM, including protein deposition-related skin lesions (amyloidosis, cryoglobulinaemia), PG, leucocytoclastic vasculitis, SS and others. However, the relationship between MM and PG is unclear.^{9 10} It seems that PG is most commonly associated with monoclonal gammopathy, and it has been detected in 10%–20% of PG cases.⁹ IgA is the paraprotein in the majority of cases.^{9–13} This could imply the existence of a pathogenic liaison, since IgA can impair neutrophil chemotaxis in vitro by blocking the surface receptors of neutrophils or monocytes.^{9 10} The coexistence of PG and IgG paraproteinaemia, however, is less common. There were three cases of association of gammopathy and PG in the literature.^{9 11 14} In one case, the monoclonal gammopathy was not associated with MM.¹⁴ In the others, PG and MM were diagnosed simultaneously. The patients responded to MM treatment (thalidomide plus dexamethasone and melphalan plus prednisolone) with resolution of PG.^{9 11}

On the other hand, there is a case report of PG associated with IgA monoclonal gammopathy of undetermined significance that was successfully treated with ASCT after trying other treatments (methylprednisolone, thalidomide, chemotherapy with vincristine, Adriamycin and dexamethasone); lesions were healed and IgA monoclonal gammopathy was no longer detected for at least 18 months.¹⁵ Patients with severe, treatment-resistant autoimmune and inflammatory diseases, such as multiple sclerosis, connective tissue diseases (particularly systemic sclerosis) and inflammatory bowel diseases, have been treated with ASCT.^{16 17} Conditioning with high-dose chemotherapy and serotherapy (such as antithymocyte globulin) delivers immunosuppression and debulking of the inflammatory load, with extensive immune re-education after eradicating the autoreactive immunological memory.^{16 17} There is also evidence of tolerance of the immune system by an increase in FoxP3-positive regulatory T cells, which may explain sustained responses following ASCT.¹⁶

Of note, some patients develop secondary autoimmune disease after ASCT, mainly those who underwent ASCT for autoimmune diseases; but new onset of autoimmune diseases has also been reported in patients having received ASCT for other indications.^{18 19} Most frequently, they are antibody-associated organ-specific autoimmune diseases, such as thyroiditis, immune thrombocytopaenia, autoimmune haemolytic anaemia and myasthenia gravis.^{18 19} The phenomenon is not unique to ASCT; it is well described in alemtuzumab-treated patients with MS, and may represent an immune reconstitution syndrome.^{16 18} The initial recovery of T-lymphocyte count in the peripheral blood is due to homeostatic expansion, and depending on the T cell subsets and prevailing conditions, such as infections, an autoimmune process may be set.¹⁸ Mechanisms for development of a secondary autoimmune disease may be related to proliferation of autoreactive cells by homeostatic expansion, as well as loss of peripheral tolerance after conditioning (by deletion of regulatory cells), failure of negative selection during de novo thymic ontogenesis of T lymphocytes or accumulation of mutations during increased proliferation of lymphocytes after ASCT.^{18 19} The immune system is substantially disturbed after ASCT; the ensuing immune reconstitution is influenced by multiple factors, many of which are unknown.¹⁸

To our knowledge, this is the first case in the literature of PG after ASCT. It is difficult to assure the role of ASCT in the aetiology of PG. Our patient had a systemic disease that could be associated with it, even though the last assessment showed no active MM. He was submitted to abdominal surgery, which has been associated more frequently with PG (PSPG). In contrast to PG and its historic systemic disease association of 50% to 78%, most patients with PSPG have no underlying disorder.² Conceivably, different factors combined are associated with the development of PG in our case. However, it is unsettlingly to have the onset of an autoinflammatory disease just after ASCT, considering the immunosuppressed state of the patient.

There are cases of PG after solid tumour transplants, such as liver and kidney in use of immunosuppressors.^{20–22} There were also two cases after allogeneic stem cell transplants.^{23 24} It was arguable in those cases that the immunosuppression associated with the transplants, both solid and haematological tumours, could play an aetiological role in the onset of PG, maybe due to

Learning points

- ▶ Pyoderma gangrenosum (PG) is a rare disease; it may be associated with systemic conditions, notably inflammatory bowel diseases, haematological malignancies and rheumatological disorders, or be idiopathic.
- ▶ Operative trauma and pathergy, likely through upregulation of neutrophils, seem to be additional driving forces in postoperative PG.
- ▶ The relationship between multiple myeloma and PG is unclear; PG is most commonly associated with monoclonal gammopathy. IgA is the paraprotein in most cases.
- ▶ Even though conventional treatment involves the use of immunosuppressive agents, cases of patients under immunosuppressive therapy who developed PG have been reported.
- ▶ Immunological impairment is caused by autologous stem cell transplantation, and this can play a role in the development of PG.

an immunological impairment caused by some immunosuppressors.^{20 23} In immunosuppressed patients, PG is extremely rare; as its conventional treatment involves the use of immunosuppression.²² In spite of this, cases have been reported. Further understanding of the pathogenesis of PG and of the effects of immunosuppression in the immune system might help to better elucidate these cases.

Contributors MJA and MCB prepared the manuscript draft and revised the literature with important intellectual input from SFC. After preparation, the manuscript was revised by EMX. All authors approved the final manuscript. All authors also were actively involved in the care of the patient. EMX conducted prehaematopoietic stem cell transplantation evaluation. MJA, MCB and SFC participated in the management of the patient's complications during his laparoscopic cholecystectomy.

Competing interests None declared.

Patient consent Next of kin consent obtained.

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