Case report

Atypical neutrophilic panniculitis as presentation of BCR-ABL1-negative chronic myeloid leukaemia

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SUMMARY

We report the case of an otherwise healthy 60-year-old man presenting with fever, leucocytosis and a painful swelling of the right calf. We initially performed cultural and cytological examination of the popliteal fossa mass, but the results were disappointingly inconclusive. The subsequent development of several erythematous subcutaneous nodules, rapidly evolving to broad ulcerative lesions, prompted us to reconsider the clinical setting as a whole, which included fever, marked leucocytosis and multiple subcutaneous nodules. A biopsy of the ulcerative lesions finally led to the diagnosis of neutrophilic panniculitis, which was sustained by a hybrid myelodysplastic/myeloproliferative disorder like BCR-ABL1-negative atypical chronic myeloid leukaemia. The patient was initially treated with high-dose intravenous corticosteroids, resulting in a dramatic improvement of the skin lesions and normalisation of blood tests. Azacytidine treatment was subsequently started, and the haematological disease remained stable.

BACKGROUND

Neutrophilic dermatoses are a group of inflammatory skin disorders that are frequently associated with haematological neoplasms, including acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS). The prototypical neutrophilic dermatosis, sweet syndrome (SS), is characterised by fever, leucocytosis and multiple tender, firm and erythematous nodules which progress into edematous plaques.¹

Pyoderma gangrenosum (PG) is another infrequent neutrophilic dermatosis for which four main variants have been described. The bullous variant, typically associated with myeloid disorders, may be clinically as well as histologically indistinguishable from SS.²

Similarly, to neutrophilic dermatoses, neutrophilic panniculitis has been more recently reported to be associated with a variety of myeloid disorders, including AML and different MDS.³

To our knowledge, we report the first case in which an ulcerative form of neutrophilic panniculitis, mimicking PG, disclosed a rare myelodysplastic/myeloproliferative disorder (MDS/MDN), such as atypical chronic myeloid leukaemia.

CASE PRESENTATION

A 60-year-old man was referred to our department for a 1-week history of high fever (up to 39°C) with an abrupt onset, associated with the development

of a painful swelling of the right calf that hampered his walking.

On admission, he reported no fatigue, weight loss, sweating, itching or joint pain. The patient had no significant current or medical history and did not take any medication. He was an active smoker, lived alone, had no contacts with children or domestic pets and did not travel abroad in the last months.

Clinical examination revealed a firm and tender oval mass below the popliteal fossa, deeply anchored to the underlying muscles of the calf. There were no signs of animal or tick bites in the overlying skin. Physical examination was otherwise unremarkable.

The routine blood tests showed a mild macrocytic anaemia (10.8 g/dL, MCV 110 fL), a marked neutrophilia (30 000/mm³) and a marked increase of C reactive protein (CRP, 15.7 mg/dL).

A point-of-care ultrasound of the right calf showed an oval mass amidst the muscle layer with a hive-like structure and a suspect semiliquid content; there were no signs of deep vein thrombosis (DVT).

A subsequent MRI confirmed these findings, providing no further clues for the working hypotheses, that, anchoring to the popliteal mass, included a septic fever due to a subcutaneous abscess, or, alternatively, a neoplasm originating from a muscular or extra-articular structure.

After the admission, daily fever persisted without a peculiar pattern, poorly responsive to intravenous acetaminophen. Blood cultures, that were drawn several times, resulted negative. The oval mass markedly swelled during the subsequent days, becoming very painful and gradually compressing the veins of the popliteal fossa, eventually causing a DVT that required anticoagulation.

Since a soft tissue abscess was our primary concern, we disappointingly attempted to drain the right calf mass percutaneously and prescribed broad spectrum antibiotics immediately after the procedure. After a few days, though, both cultural and cytological examination turned out to be negative.

Besides a slight decrease in intensity in the ensuing days, high fever relapsed in a short while despite antibiotic treatment. Blood tests showed a further increase of leucocytes (57.3×10⁹/L), with the presence of circulating immature granulocytes. Anaemia worsened and required a transfusion of packed red blood cells.

Unexpectedly, 3 weeks after the onset of fever, several painful and erythematous to violaceous skin nodules developed, most of them involving the lower limbs (figure 1A). On examination, the nodules were firm and tender, apparently infiltrated.

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Figure 1 (A) The appearance of the several tender, firm and erythematous subcutaneous nodules in the lower limbs of the patient and (B) the evolution of the nodules into a broad ulcerative lesion after a few days.

Most of them enlarged evolving within days into broad ulcerative lesions with a violaceous undermined margin ([figure 1B](#)).

DIFFERENTIAL DIAGNOSIS

This new sign allowed a proper reframing of the problem representation: an adult man presenting with high fever, marked leukocytosis and multiple cutaneous nodules prone to ulceration.

Our differential diagnosis included cellulitis-like infections, panniculitides, neutrophilic dermatoses, vasculitides and haematological malignancies.

Among bacterial infections, *Treponema* and *Nocardia* may present with nodular lesions. Fungal infections and atypical mycobacteriosis could also affect skin with nodular lesions, but these are usually seen after systemic dissemination in an immunocompromised host.

The term panniculitis refers to a wide spectrum of diseases in which an inflammatory infiltrate collects in the subcutaneous layer. This infiltrate could be secondary to an infection by bacteria or, less frequently, by mycobacteria, although most cases of infective panniculitis occur in the setting of immunosuppression or systemic spread of an infection. As well, many non-infectious causes of panniculitis such as *erythema nodosum* are commonly recognised. *Erythema nodosum* (EN), the most common non-infectious panniculitis, is an acute nodular eruption that may be idiopathic or related to enteropathies, haematological neoplasms and granulomatous diseases such as sarcoidosis. However, EN rarely ulcerates.

Among neutrophilic dermatoses, we considered SS and PG to be equally likely. Although atypical, SS lesions may sometimes ulcerate, especially in the setting of myeloid disorders. Some Authors described the so called 'neutrophilic dermatosis of myeloproliferative disorders' as an atypical form of PG and SS associated with myeloproliferative disorders and proposed that they may represent points on a continuum of non-infectious, non-metastatic, inflammatory neutrophilic dermatoses.

Among systemic vasculitides, *polyarteritis nodosa* (PAN) involves medium calibre arteries and it is highly prevalent in patients with Hepatitis B virus (HBV) infection. PAN-related cutaneous involvement usually presents with palpable and painful subcutaneous nodules that may sometimes ulcerate.

Among malignancies, some rare forms of primary cutaneous diffuse large B-cell lymphomas may present with nodular lesions.

Moreover, another common primary cutaneous lymphoma is T-cell mycosis fungoides, which generally presents with erythematous itching plaques.

Further diagnostic tests were requested to narrow the differential diagnosis. Serum autoantibodies, such as antinuclear antibodies and anti-neutrophil cytoplasmic antibodies, resulted negative, as were rheumatoid factor and tests for *Treponema pallidum* and the purified protein derivative skin test for *Mycobacterium Tuberculosis*. Tests for hepatitis B resulted negative for present or past infection. Faecal calprotectin resulted within normal range, and peripheral blood lymphocyte phenotyping showed a normal polyclonal pattern. Finally, an abdominal and thoracic CT scan was negative for the presence of malignancies or lymphadenopathies.

After this workup, our leading hypothesis was a neutrophilic dermatosis or, alternatively, a non-infectious panniculitis. In order to obtain a histopathological characterisation, we performed a surgical biopsy, sampling a large ulcer of the left leg at the margin of the lesioned skin.

The specimen showed the infiltration of the subcutaneous septal and lobular fat with neutrophils and histiocytes, without signs of vasculitis and with a normal appearance of the superficial dermis. Cultures of the tissue were negative for bacteria (including acid-fast bacilli) and fungi. These features were primarily consistent with a neutrophilic panniculitis ([figure 2](#)).

Among neutrophilic panniculitides, features like fever and marked leucocytosis favoured the diagnosis of subcutaneous SS may, even if the ulcerative evolution and the deep tissues involvement is also common in PG.

Given the strong association between both neutrophilic dermatoses and panniculitides and haematological malignancies, we requested a bone marrow biopsy. The histopathological examination was suggestive of a hybrid MDS/MDN ([figure 3](#)), whereas karyotype and fluorescent in situ hybridisation confirmed the presence of trisomy 8. Since translocation of BCR-ABL was negative, the disorder had been classified as a BCR-ABL1-negative atypical chronic myeloid leukaemia.⁴

TREATMENT

The prompt treatment with high-dose intravenous corticosteroids resulted in a dramatic improvement of the skin lesions and normalisation of leucocytes (6180/mm³).

Figure 2 (A, B) Skin biopsy section showing a moderate inflammatory process in the septal and lobular hypodermis, predominantly composed of histiocytes and neutrophils; no signs of vasculitis were present (H&E, A $\times 10$ and B $\times 20$) and (C) immunohistochemical staining showing the presence of CD68/PGM1 positive histiocytes ($\times 20$).

The patient was thereafter referred to the haematology consultant. After a few days, the patient started azacytidine treatment.

OUTCOME AND FOLLOW-UP

Despite haematology recommendation, the patient refused to undergo allogenic bone marrow transplantation. After 6 months of azacytidine treatment, the cutaneous disease has not relapsed and the haematological disease was stable. At the latest follow-up, 2 years from onset, the haematological disease is still stable and the skin lesions are in steroid-free remission.

Figure 3 Bone marrow trephine biopsy sections showing a markedly hypercellular marrow, expansion of granulopoiesis with abundant segmented neutrophils and slight left shifted maturation. Immature precursors reactive for CD34 were scant (H&E, $\times 20$). The whole picture was consistent with a myeloproliferative neoplasm like chronic myeloid leukaemia or a hybrid myelodysplastic/myeloproliferative neoplasm featuring atypical chronic myeloid leukaemia.

DISCUSSION

In our patient, the clinical picture initially pointed towards a typical neutrophilic dermatosis such as SS.¹ However, the whole scenario turned out to be quite atypical, since most of the nodules ulcerated in a short while. The formation of an ulcer is quite uncommon in SS, even in its subcutaneous variant,³ but it is rather a typical behaviour of PG-like lesions. Another feature that hinted to PG was the lower limbs predominance of the lesions. Histologically, the specimen showed signs of neutrophilic panniculitis, which is not a common aspect of PG-like lesions but rather a possible feature of the rarer subcutaneous variant of classical SS. Taken together, the clinical and histopathological data of our patient favoured the diagnosis of subcutaneous SS, although we could not definitely exclude an atypical form of SS or PG secondarily extending to the hypodermis.³

Subcutaneous SS is an uncommon variant of classic SS that involves the hypodermis sparing the dermal tissues. Subcutaneous SS is included in the group of neutrophilic panniculitides, along with many other entities such as infectious panniculitis, early-developed *erythema nodosum*, pancreatic panniculitis, alpha1-antitrypsin deficiency panniculitis, *erythema induratum* and rheumatoid arthritis associated panniculitis.³

Although the association of neutrophilic dermatosis with haematological malignancies is well known, only in recent years neutrophilic panniculitis, especially subcutaneous SS, has been recognised as another frequent cutaneous manifestation of myeloid diseases. In particular, several cases of subcutaneous SS associated with AML and different MDS have been reported.² Usually, the typical presentation of subcutaneous SS in these patients closely resembles that of classic SS.

Conversely, an atypical presentation of a neutrophilic dermatosis is not uncommon in patients with an underlying haematological disorder. Indeed, Caughman and coworkers even suggested to name this peculiar condition 'neutrophilic dermatosis of myeloproliferative disorders', since in these cases the

inflammatory lesions may range from typical neutrophilic dermatoses to variants with extensive ulceration, representing a continuum in a dynamic neutrophil-mediated process.⁵

In conclusion, we reported the first case of neutrophilic panniculitis associated with an MDS/MDN like BCR-ABL1-negative atypical chronic myeloid leukaemia.

Learning points

- ▶ Neutrophilic panniculitis can occur with a variety of myeloid disorders, including BCR-ABL1-negative atypical chronic myeloid leukaemia.
- ▶ The presentation of neutrophilic panniculitis is highly heterogeneous and biopsy is usually required to confirm clinical suspicion.
- ▶ The development of cutaneous ulcerations with a neutrophilic infiltrate should raise suspicion of an underlying myeloid neoplasm.

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