

CASE REPORT

Paraneoplastic leukemoid reaction in a patient with BRAF V600E-mutated metastatic malignant melanoma

Emanuel Gouveia, Mónica Sousa, Maria José Passos, António Moreira

Medical Oncology Department
Instituto Português de
Oncologia de Lisboa Francisco
Gentil, Lisboa, Portugal

Correspondence to

Dr Emanuel Gouveia,
emgouveia@hotmail.com

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SUMMARY

A paraneoplastic leukemoid reaction is a rare condition of extreme leucocytosis in patients with solid malignancies. The differential diagnosis is often a true challenge. We present a case of a 56-year old woman with a history of stage IIIA malignant melanoma resected in 2004 that was diagnosed in May 2013 with BRAF V600E-mutated metastatic disease (left arm mass, lungs and adrenal glands). The laboratory findings revealed leucocytosis with granulocytosis that increased progressively to values up to $120.0 \times 10^9/L$. After a diagnostic work-up, a diagnosis of a paraneoplastic leukemoid reaction was established. We report the response of leucocytosis to radiation and BRAF inhibitor therapy, albeit short-lived. To the best of our knowledge, this is the first case report of a paraneoplastic leukemoid reaction in metastatic melanoma with characterisation of BRAF V600 mutation status. It remains unclear whether the aggressive tumour phenotype is related to the leukemoid reaction and whether this is related to the BRAF mutation.

BACKGROUND

A paraneoplastic leukemoid reaction is a rare condition of extreme leucocytosis occurring in patients with solid malignancies. The major causes of a leukemoid reaction (usually defined as a persistent leucocytosis greater than $50 \times 10^9/L$) include malignancies, severe infections, intoxications, corticosteroid administration, severe haemorrhage and acute haemolysis.^{1 2} The differential diagnosis of a leukemoid reaction in patients with cancer is often a true challenge. Diagnostic work-up in these patients must rule out other underlying causes such as infection and acute and chronic leukaemia. A paraneoplastic leukemoid reaction has been reported in several solid tumour types and appears to be associated with a poor prognosis.^{3–9} Malignant melanoma has been associated with a variety of paraneoplastic manifestations including hormonal and dermatological syndromes.¹⁰ Some previous reports have described the extraordinarily rare occurrence of a paraneoplastic leukemoid reaction in patients with metastatic malignant melanoma.^{11–14} The underlying mechanism of paraneoplastic granulocytosis in melanoma and in other solid malignancies is the abnormal secretion of cytokines such as granulocyte colony-stimulating factor (G-CSF).^{13 15 16} Although previous reports have suggested that this is related to rapid disease progression, it is still unclear whether the

paraneoplastic process is indicative of an aggressive tumour phenotype.^{13 16} It also remains unclear if this is related to different responses to therapy. As far as we know, this is the first report of a paraneoplastic leukemoid reaction related to BRAF-mutated metastatic melanoma and its response to radiotherapy and the BRAF inhibitor.

CASE PRESENTATION

A 56-year-old woman presented in April 2013 with severe persistent pain and an abnormal swelling in her left arm. Nine years earlier (in 2004), she was subjected to excision of a right leg superficial spread malignant melanoma, Breslow 1.52 mm, with no ulceration. Sentinel lymph node biopsy was positive and she underwent right inguinal lymph node dissection, with seven negative nodes. The thoracic, abdominal and pelvic CT (TAP-CT) did not reveal distant metastasis (stage IIIA, American Joint Committee on Cancer (AJCC) 7th edition). Seven years later in 2011, the patient was found to have a local recurrence and underwent surgery. Until 2013, she had always had a normal white cell count (WCC). Her medical history was unremarkable apart from the melanoma, and there was no history of corticosteroid consumption. Owing to the pain in the left arm, a plain radiography was performed that revealed a suspicious humeral lesion (figure 1). A bone scan confirmed a single bone metastasis in the left humerus. She was referred to our medical oncology department and a CT-guided biopsy to the left arm lesion was performed, revealing BRAF V600E-mutated malignant melanoma metastasis (cobas® 4800 BRAF V600 Mutation Test). The staging TAP-CT showed a soft-tissue large mass (130×100 mm) involving the humerus with bone destruction and vessel incarceration (figure 2) and also bilateral lung and adrenal metastasis. Laboratory findings at this time included: haemoglobin (Hb) 12.4 g/dL, platelet count $315 \times 10^9/L$, leucocyte count $40.2 \times 10^9/L$, neutrophils $36.5 \times 10^9/L$ (91%), lymphocytes $2.21 \times 10^9/L$ (5.5%), increased lactate dehydrogenase 424 UI/L, increased alkaline phosphatase 183 UI/l and C reactive protein (CRP) levels not elevated. There was neither fever nor signs of infection. The patient was given four cycles of chemotherapy with dacarbazine 1000 mg/m^2 on day 1 every 21 days with dexamethasone as a prophylactic antiemetic for 3 days after each cycle of chemotherapy. After the fourth cycle of dacarbazine, there was an increase of the swelling (figure 3) and worsening pain in the left



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Figure 1 Plain radiography revealing a left humeral lesion with marked bone erosion.

arm requiring increasing doses of opioid analgesics. The reevaluation scan performed at this time revealed a mixed response, with an increase of the left arm lesion and reduction in the size of pulmonary and adrenal metastasis. The leucocytosis increased during chemotherapy from a leucocyte count of $65.4 \times 10^9/L$ to $120.0 \times 10^9/L$ (figure 4), with neutrophil predominance (93–97%) and macrocytic anaemia developed (Hb range 7.3–8 g/dL; mean corpuscular volume 105.2 fL). The patient remained afebrile and without any signs of infection, and a peripheral smear demonstrated marked leucocytosis primarily attributable to mature neutrophils. Bone marrow biopsy showed hypercellular bone marrow with all cell lines represented, with a marked right shift in granulopoiesis. There was no infiltration by melanoma tumour cells (figure 5). Testing for BCR/ABL1 translocation and the JAK2 V617F mutation were negative. A diagnosis of a paraneoplastic leukemoid reaction was then established.

Owing to the increasing pain, the patient was subsequently treated with external-beam radiotherapy to the left arm lesion (30 Gy in 10 fractions). After the radiotherapy, there was a slight improvement in the swelling, and in a few weeks the patient reported that her pain intensity lessened for lower levels allowing a reduction of opioid dosages. Over the same period,

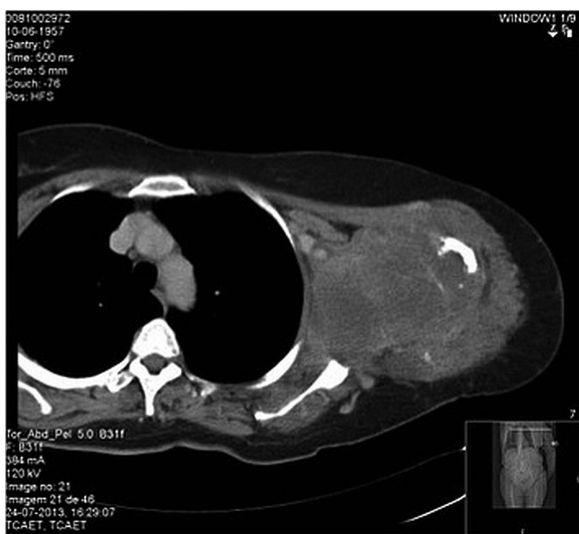


Figure 2 Soft-tissue mass involving the humerus with bone destruction.



Figure 3 Left arm clinical appearance after four cycles of chemotherapy with dacarbazine.

there was a significant reduction in the WCC levels from $110.0 \times 10^9/L$ (at the beginning of radiation therapy) to 49.0×10^9 in the next 4 weeks after treatment completion (figure 4). Unfortunately, the radiotherapy effect was of short duration and the pain worsened, as well as the swelling. After the national regulatory drugs authority approval, the patient started vemurafenib 960 mg twice daily initially with rapid improvement in the left arm swelling. After 15 days of treatment with vemurafenib, the laboratorial evaluation revealed a significant fall in the WCC to normal values ($7 \times 10^9/L$) (figure 4). Moreover, as observed previously with radiotherapy, there was an improvement of anaemia. In the first month, there were no major toxicities with this drug. However, after 2 months of objective clinical response to vemurafenib, an impressive ulceration of the lesion on the left arm occurred and an exudate emerged (figure 6). She reported no fever and there were no other obvious infection sites. By this time, antibiotic therapy was started first with a second-generation cephalosporin and next with trimethoprim-sulfamethoxazole with slight improvement. Exudate and blood cultures were negative. Over the same time period, the patient presented with grade 3 mucositis, which justified the interruption of the BRAF inhibitor for 15 days. After mucositis resolution, vemurafenib was resumed at 720 mg twice daily dose. During the next 2 months, the leucocytosis increased to 83.3×10^9 (figure 4). The patient's condition worsened with progressive fatigue, increasing pain and a rapidly increasing haemorrhagic malignant wound. Owing to the rapid

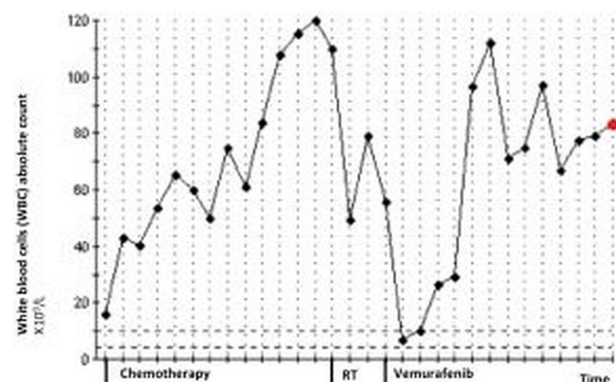
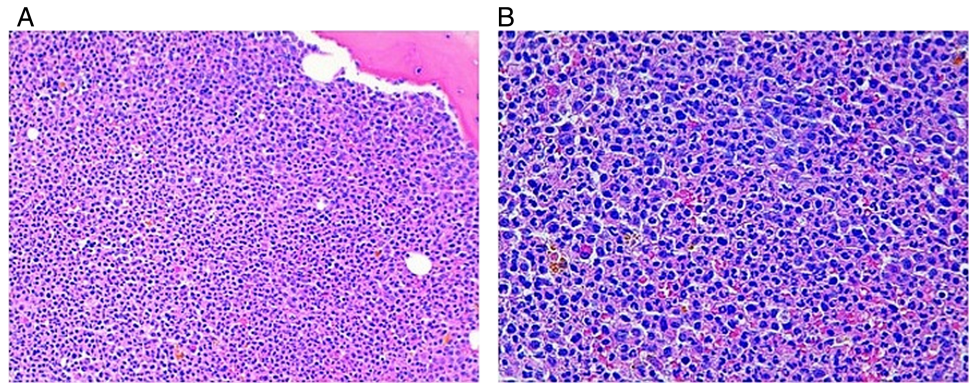


Figure 4 Evolution of white cell count since metastatic disease diagnosis until the patient's death.

Figure 5 (A and B) Bone marrow biopsy with all cell lines represented, a marked right shift in granulopoiesis and no evidence of melanoma tumour cells.



deterioration of performance status, vemurafenib was permanently discontinued. She was admitted in our oncology department ward and single dose radiotherapy to control bleeding was considered but not performed due to the patient's condition.

OUTCOME AND FOLLOW-UP

Unfortunately, her clinical condition continued to deteriorate and she died 5 days after admission.

DISCUSSION

Paraneoplastic syndromes are rare events that result from the indirect effect of cancer through the production of humoral, neural or immune factors including cytokines, protein hormones or antigen-antibody interactions. Previous reports have described the occurrence of paraneoplastic manifestations in metastatic malignant melanoma such as dermatological and hormonal syndromes.¹⁰ Haematological manifestations are common in solid malignancies, most frequently cytopenias. The underlying causes for cytopenias in cancer include the tumour infiltration of bone marrow, the effects of chemotherapy and radiation therapy and the chronic disease condition by itself. The abnormal elevation of blood cell counts, including

leucocytosis is less frequent. A leukemoid reaction is defined as a persistent leucocytosis greater than $50 \times 10^9/L$ and can be neutrophilic or lymphocytic. This condition is observed in a variety of clinical settings. Causes of a neutrophilic leukemoid reaction include infections, intoxications or medications (eg, steroids, G-CSF therapy and mercury poisoning), serious burns, haemorrhage and acute haemolysis.^{1 2} Besides all these causes, the diagnostic work-up requires the exclusion of haematological diseases like chronic myelogenous leukaemia (CML) and myeloproliferative disorders. It is also crucial to rule out bone marrow invasion and replacement with metastatic solid tumour cells causing a leucoerythroblastic picture. In our patient, infectious causes were considered unlikely when leucocytosis first appeared. She remained afebrile, there were no evident signs of obvious infection and CRP was not increased. When the first signs of wound infection appeared in the left arm, leucocytosis was already established. Exudate and blood cultures also remained sterile. We also thought it was unlikely that the dosage of corticosteroids was responsible for causing leucocytosis. Moreover, although the patient was treated with antibiotics, the leucocytosis remained unchanged. She was not taking any medication possibly associated with a raised WCC. Given the size of the left arm mass and rapid growth, tumour necrosis could be a possible cause of leucocytosis. However, since CRP was not increased, this hypothesis was unlikely. We performed a peripheral smear that revealed marked leucocytosis that was primarily attributable to mature neutrophils. Additional investigation included bone marrow biopsy and testing for BCR/ABL1 translocation and the JAK2 V617F mutation. The bone marrow biopsy excluded infiltration by malignant melanoma cells and revealed characteristics consistent with hyperstimulation of granulopoiesis. The diagnosis of CML was very unlikely due to the absence of BCR/ABL fusion on cytogenetics and the normal basophil count. Similarly, negativity of the JAK2 mutation made the diagnosis of myeloproliferative disorders unlikely. Likewise, other less obvious causes of the leucocytosis listed were excluded. The presumptive diagnosis of a paraneoplastic leukemoid reaction was thus established.

A paraneoplastic leukemoid reaction has been described in a variety of malignant solid tumours including, among others, bladder carcinoma, sarcoma, lung cancer and cervical carcinoma.³⁻⁹ This event is extraordinarily rare in patients with melanoma, with only a few cases reported in the literature.¹¹⁻¹⁴ In a study conducted in 626 patients with metastatic melanoma, Davis *et al*¹⁴ point out the rarity of paraneoplastic granulocytosis in this population, with only six patients presenting an elevated WCC and significantly elevated serum G-CSF levels. Most commonly, the secretion of G-CSF has been reported as the predominant mechanism of a leukemoid reaction in solid



Figure 6 Left arm ulceration.

malignancies. G-CSF was indeed first purified from a bladder carcinoma cell line.¹⁷ Malignant melanoma has also been reported to secrete G-CSF. In 1987, Lilly *et al*¹⁵ reported that a human melanoma cell line (LD-1) was isolated from a patient with melanoma and unexplained leucocytosis. In this report, production of G-CSF in vitro was confirmed by molecular studies. Later in 2005, Schniewind *et al*¹³ reported the rapid progression of a patient with metastatic malignant melanoma with a paraneoplastic leukemoid reaction. This patient presented an elevated serum G-CSF level and the investigators isolated a G-CSF secreting melanoma cell line (KT293). They suggested that the paracrine effects of G-CSF secretion and a paraneoplastic leukemoid reaction might promote an aggressive disease phenotype.¹³ Safarians *et al*¹⁶ have suggested the same in an in vitro study that hypothesised G-CSF expression in human melanoma cell lines as a marker of a pathway linked to tumour progression and metastasis. In this study, Safarians *et al* ruled out an autocrine mechanism, noting the absence of G-CSF receptors in the G-CSF secreting melanoma cells. In other case reports, the paraneoplastic leukemoid reactions in distinct malignancy types have also been associated with worse prognosis, although the link between rapidly progressing cancer and leukemoid reactions has not been clearly established.^{6 7 13} In our case report, we pointed out the aggressiveness of the disease and rapid progression despite chemotherapy and BRAF inhibitor therapy. This is confirmed by those reports of a possibly more aggressive disease phenotype in patients with a leukemoid reaction. It remains unknown to what extent this phenotype of aggressive malignant melanoma is related to the presence of BRAF V600 mutation or other mutations (eg, NRAS, cKIT). As far as we know, this is the first case of a paraneoplastic leukemoid reaction in metastatic melanoma with characterisation of BRAF V600 mutation status, since this was not available at the time of the previous reports. Another interesting point in our case is the link between clinical response to radiotherapy and BRAF inhibitor therapy and lowering of WCCs. In the case of palliative radiotherapy, there was a positive tumour effect, albeit short-lived. It remains unclear what is the mechanism by which local control of the primary site of disease leads to an improvement of leukemoid reaction. After initiation of therapy with vemurafenib, the decline in WCCs was extremely rapid, reaching normal levels within 15 days. Unfortunately, the clinical response was also short-lived and there was a progressive increase in WCC that accompanied the patient's clinical deterioration. Some previous reports have noted that the monitoring of WCCs could be an indicator of tumour response to chemotherapy or radiotherapy or, on the contrary, a marker of recurrence.^{8 9} A previous report by Carey and Kunz¹¹ in 1988 related the reversal of leucocytosis after bilateral adrenalectomy in a patient with malignant melanoma with adrenal metastases, and this was related with improved survival. Interestingly, our patient also presented with bilateral adrenal metastasis. However, we report for the first time the response of a paraneoplastic leukemoid reaction to radiation and BRAF inhibitor therapy in a patient with BRAF V600E-mutated metastatic melanoma, albeit short-lived. Unfortunately, a more detailed molecular analysis of our patient's tumour cell lines was not performed. It remains uncertain why some melanoma cell lines secrete G-CSF and whether this is related to already known mutations (eg, BRAF, NRAS and cKIT). It is also unclear whether there are different mechanisms of resistance to therapy in these particular cases, leading to a poor response or responses of shorter duration. These hypotheses need further investigation.

Learning points

- ▶ A paraneoplastic leukemoid reaction is extremely rare in patients with malignant melanoma, and the differential diagnosis is often a true challenge.
- ▶ We report the first case described of a paraneoplastic leukemoid reaction in metastatic melanoma with characterisation of BRAF V600 mutation status and the response of leucocytosis to radiation and BRAF inhibitor therapy, albeit short-lived.
- ▶ In line with previous reports, we describe an aggressive tumour phenotype related to a leukemoid reaction.
- ▶ It remains unclear whether the aggressive tumour phenotype is related to a leukemoid reaction and whether this is related to the BRAF mutation.

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Competing interests None.

Patient consent Obtained.

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