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CASE REPORT

Extreme leucocytosis and splenomegaly in metastasised melanoma

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ABSTRACT

A 63-year-old woman presented to the internist with fatigue, cough, low-grade fever, splenomegaly and leucocytosis up to 130 x 10^9/l. Although a diagnosis of chronic myelogenous leukaemia was initially entertained, she turned out to have a metastasised melanoma.
The differential diagnosis and workup is discussed, as well as potential mechanisms by which the tumour could have induced the leucocytosis, such as the production of G-CSF or similar mediators, and the prognostic significance of this phenomenon.

CASE REPORT

A 63-year-old woman was referred to the internist because of progressive fatigue and breathlessness for several months. She even got breathless from talking. She had lost 15 kg of weight and had intermittent fevers up to 38.6°C. There were no night sweats. Several courses of oral broad-spectrum antibiotics had not had any effect on her symptoms. The previous medical history was unremarkable apart from an unspecified lung operation at the age of 13 and chronic obstructive pulmonary disease. Ten months earlier a melanoma had been removed from her left ankle, histologically Breslow depth 1.5 mm and Clarke level III. Her medication consisted of inhaled bronchodilatators, steroids and acetylcysteine. The family history included a brother with multiple sclerosis and a brother with colonic carcinoma. On physical examination a pale and breathless woman was seen. She was 1.65 m tall and her weight was 60.3 kg. The pulse was 100 beats/min, blood pressure 120/70 mmHg and rectal temperature 39.0°C. There were no enlarged lymph nodes and no pathological findings of heart and lungs. No breast lumps were palpable. Her liver was palpable under the right costal margin and the spleen was palpable 10 cm under the left costal margin. There was no peripheral oedema and no other findings at the extremities.
Laboratory findings were: Hb 5.5 mmol/l (8.91 mg/dl), thrombocyte count 377 x 10^9/l, leucocyte count 62.4 x 10^9/l (differential: neutrophils 73%, eosinophils 11%, basophils 0%, lymphocytes 11%, monocytes 4%, some metamyelocytes and myelocytes; erythroblasts were not observed). The electrolytes and renal function were normal. Liverfunction tests: ASAT 21 U/l, ALAT 12 U/l, LDH 527 U/l, alkaline phosphatase 295 U/l, γGT 196 U/l, ferritin 379 µg/l and serum iron 3.1 µmol/CRP was elevated at 101 mg/l.

Bone marrow biopsy showed hypercellular bone marrow with all cell lines represented, though a strong increase in granulopoeisis was seen. Occasionally some very atypical cells were seen with polymorphic hyperchromatic nuclei, a coarse chromatin pattern and enlarged nucleoli.
Bone marrow cytology showed an increased granulopoeisis (70%) with moderate left shift, 2% blasts, increase of eosinophilic elements (14%) with multiple precursors. There was decreased erythropoiesis and megakaryopoiesis. Scattered through the marrow there were large, very atypical cells with an epitheloid aspect, one or more round to oval nuclei, abundant cytoplasm which sporadically contained blue-grey granula (see *figure 1*). These cells were identified as (amelanotic) melanoma cells.

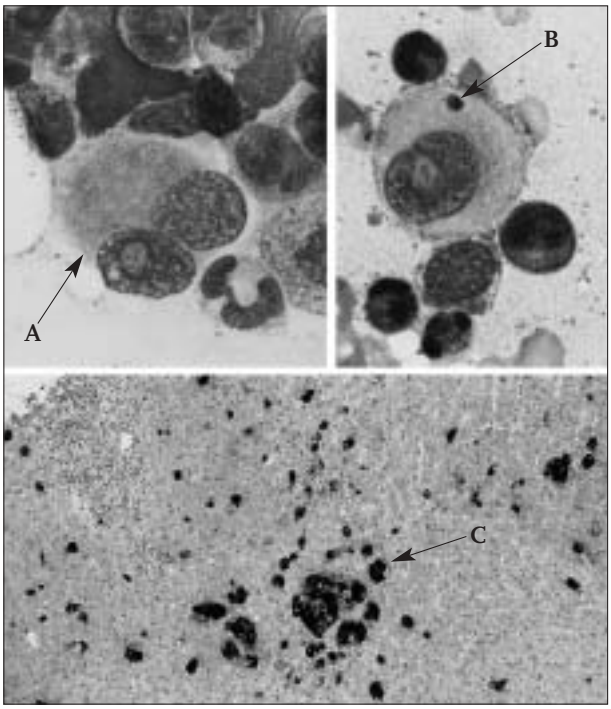

Figure 1
Microscopy
Top: Bone marrow aspirate with large, very atypical cells with an epitheloid aspect, one or more round to oval nuclei (A), abundant cytoplasm containing sporadic blue-grey granula (B).
Bottom: Liver biopsy (HMB-45 and S100 staining) with agglomerates (C) of melanoma cells and marked hypergranulocytosis of the sinuses.

Cytogenetics showed 20 cells with a normal female karyotype and no *bcr-abl* fusion on fluorescent *in situ* hybridisation (FISH) in ten metaphases.
Blood cultures (two separate 3-10 ml aliquots containing aerobic and anaerobic media) were negative. Mid-stream urine examination showed several leucocytes per high-power field and upon culture contained mixed bacterial flora. Sputum was negative for auramine and Ziehl-Neelsen staining but on culture showed *Haemophilus parainfluenzae*.
Ultrasound examination of the abdomen showed an enlarged liver with multiple lucencies, a very large spleen of 20 cm with one lucency possibly due to metastasis, some ascites and no enlarged lymph nodes.
Computed tomography (CT) of chest and abdomen showed no signs of a primary tumour, signs of infiltration in the left lower pulmonary lobe, many metastases in the liver and a solitary one in the spleen, one pathological lymph node around the abdominal aorta and some ascites.
Ultrasound-guided biopsy of one of the liver lesions showed disseminated melanoma cells in small clusters and marked granulocytosis of the sinusoids. Immunohistochemical staining was positive for melanoma (HMB-45, S100, Schmorl's stain weak).
During the stay in hospital the leucocytosis increased to 130.3 x 10^9/l despite antibiotic therapy and the patient's condition worsened with night sweats and progressive fatigue. She declined chemotherapy, and was released with terminal home care; she died at home one day after discharge. A postmortem examination was not performed.

DISCUSSION

Extreme leucocytosis can be caused by infection, malignancy and several other, less common causes. When leucocyte counts exceed 50 x 10^9/l it is referred to as 'leukaemoid reaction' (see *table 1*). Reding *et al*. studied 100 patients presenting with leucocytosis exceeding 25 x 10^9/l and found infection as a cause in only 48%.[1] In 15% malignancy was diagnosed and in the remaining 37% other, less common secondary causes were found (such as haemorrhage, glucocorticoid therapy, rhG-CSF therapy).

Table 1
Causes of neutrophilic leukaemoid reaction (leucocyte count >50 x 10^9/l)[1,15]

INFECTIONS
Pneumonia
Meningitis
Diphtheria
Tuberculosis
Shigellosis
INTOXICATIONS/MEDICATION
Mercury poisoning
Steroids
Adrenergic agents
All-trans retinoic acid (ATRA)
G-CSF
PHYSICAL CAUSES
Serious burns
MALIGNANCY
Bone metastasis
Multiple myeloma
Myelofibrosis
Hodgkin's disease
Other malignancy
SERIOUS HAEMORRHAGE
ACUTE HAEMOLYSIS
ECLAMPSIA
PREMATURITY/NEONATES
HEREDITARY/CONGENITAL

The leucocyte count was not predictive of the cause. The 15 patients with malignancy mostly had primary haematological disorders, but metastatic carcinoma was diagnosed in six of them.
Fatigue, splenomegaly and leucocytosis as presenting signs in a middle-aged patient all point at the possibility of myeloproliferative syndrome (MPS). However, careful review of the history, physical examination, infectious parameters (such as blood culture, chest X-ray and midstream urine specimen), blood film and bone marrow aspirate and trephine can give clues as to a secondary cause.
After excluding infectious disease and drug-related causes of leucocytosis, the diagnostic effort should concentrate on the possibility of malignancy. To differentiate between primary haematological and secondary causes, normal to low basophil granulocytes on the blood film, as well as negative cytogenetics (no t(9;22)(q34;q11) translocation causing *bcr-abl* fusion) make myeloproliferative disease very unlikely.
There are roughly two ways in which nonhaematological malignant disease can lead to leucocytosis. Firstly, bone marrow invasion by metastases can cause a leucoerythroblastic picture. Secondly, an oft-reported form of leucocytosis in malignancy is a leukaemoid reaction due to production of cytokines or other mediators by tumour cells.

In our patient, infectious causes were considered unlikely, with blood cultures remaining sterile all through the patient's stay in hospital. She was not taking any oral medication associated with a raised leucocyte blood count. The absence of *bcr-abl* fusion on cytogenetics and the normal basophil count made the diagnosis of chronic myelogenous leukaemia (CML) very unlikely (<5% of CML patients are *bcr-abl* negative).[2]
The finding of metastatic lesions of the primary melanoma in the liver biopsy, as well as malignant cells in the bone marrow, confirmed the suspected diagnosis of tumour-induced leucocytosis. Bone marrow infiltration as such was not perceived to be an explanation for the symptoms, given the absence of leucoerythroblastosis in the blood. Therefore, the diagnosis was leukaemoid reaction due to the production of a humoral factor by a primary melanoma.

Virtually every type of malignant tumour has been reported to induce leucocytosis, for example glioblastoma multiforme,[3] head and neck carcinoma[4] and malignant mesothelioma.[5] Generally the secretion of G-CSF or GM-CSF, most commonly the former,[6] by the tumour cells seems to be the predominant mechanism of the leukaemoid reaction in malignancy.[7]
Malignant melanoma has been reported to secrete G-CSF or GM-CSF,[8-11] and this feature appears to be a marker of poor prognosis.[10] In the patient reported by Carey and Kunz[11] the leucocytosis resolved when the adrenal metastases were removed through bilateral adrenalectomy. Eosinophilic leukaemoid reaction has been reported in a case of melanoma secreting extremely high quantities of IL-5.[12] Concerning the contribution of G-CSF production to a tumour's malignant potential, Safarians *et al*. found that G-CSF-secreting melanoma cells do not express G-CSFR, thereby ruling out an autocrine mechanism.[10]
Otherwise, G-CSF can stimulate endothelial proliferation and migration, thereby assuring the tumour of a steady blood supply through angiogenesis.[13] Moreover, the granulocytes themselves can benefit the tumour by inducing further malignant transformation.[14]
Finally, Safarians *et al*. suggest that the expression of G-CSF could be a side effect of the activation of other oncogenes, which increase the tumour's capability of malignant transformation, growth and dissemination.[10]

CONCLUSION

The diagnosis in this patient turned out to be metastasised melanoma with extreme granulocytosis, possibly due to G-CSF production by the tumour cells.

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