Extreme neutrophil granulocytosis in a patient with anaplastic large cell lymphoma of T-cell lineage

Case report

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We describe a 47-year-old male admitted with fever and extreme neutrophil granulocytosis (up to $80 \times 10^9/L$). All microbiology tests and test for autoimmune disease were negative. CT scan showed pulmonary infiltrates bilaterally, mediastinal lymphadenopathy and splenomegaly. Conventional pathological examination of bone marrow and lymph node biopsies did not demonstrate malignant cells and inflammatory disease was suspected. The patient died of multiorgan failure 23 days after admission. Autopsy showed neutrophil infiltration of several organs. Immunohistochemistry and cytogenetics postmortem led to a diagnosis of anaplastic large cell lymphoma (ALCL) of T-cell lineage. Involvement of peripheral blood with leukemoid reaction is a rare manifestation of ALCL. This case emphasizes the importance of immunophenotyping in unexplained extreme granulocytosis.

Key words: Leukemoid reaction; immunohistochemical staining; ALCL; infection.

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Fever and neutrophil granulocytosis are common findings in patients with severe bacterial infection. However, several non-infectious diseases may induce these two essential clinical stigmata and therefore the clinician may be presented with a major differential diagnostic challenge. We describe a patient with anaplastic large cell lymphoma (ALCL) of T-cell lineage and extreme neutrophil granulocytosis.

CASE HISTORY

A 47-year-old previously healthy male was admitted with diarrhea, nausea and fever. He had been well until 2 weeks previously. The patient had been treated with V-penicillin and doxycycline prior to admission but with no clinical effect. On admission the patient presented with bilateral small sore angular lymph glands, oral candidiasis, moderate hypoxia and diarrhea. Neurological examination was normal. The patient had neutrophil leukocytosis ($33 \times 10^9/L$; normal range $3–10 \times 10^9/L$), increased CRP (530 mg/l; normal range $<10$ mg/ml), and slightly elevated liver enzymes. Bence Jones protein in blood and urine and tests for autoimmune diseases were all negative. All microbiology tests were negative, including HIV, Epstein Barr and cytomegalovirus serology, PCR of sputum for legionella, mycoplasma and chlamydia, and cultures of bronchoalveolar lavage fluid. CT-scan of the head and neck showed a left parietal cerebral tumor, $2 \times 2.5$ cm, supposedly an oligodendroglioma, which was considered an incidental finding. CT scans of the abdomen and chest showed pulmonary infiltrates bilaterally with small exudates, discrete mediastinal lymphadenopathy not suspected of repre-
senting malignancy, and splenomegaly. The following tests initially showed no abnormality: Chest X-ray, direct laryngoscopy, ultrasound of the neck, dental examination, echocardiography, ventilation/perfusion scintigraphy and leukocyte scintigraphy. A blood smear showed leukemoid reaction, but there was no suspicion of malignant hematological disease. A bone marrow biopsy performed after 1 week was hypercellular, consistent with inflammation but without signs of hematological malignancy, which is why immunohistochemistry and cytogenetic tests were not performed. Microscopy of pleural fluid showed acute and chronic inflammatory cells and reactive mesothelial cells.

The patient developed respiratory insufficiency and exanthema on the thighs and trunk along with hemorrhagic chemosis. Repeated chest X rays showed increasing infiltration in both lungs.

Bacterial infection was initially suspected and treated with intravenous meropenem (1 g TID), ciprofloxin (400 mg BID) and capsule fluconazole (50 mg QD), supplemented with clindamycin. In spite of antibiotic treatment, leukocyte count rose to $57 \times 10^9/\text{L}$. After 9 days, treatment with Solumedrol (1 mg/kg) was initiated and the patient responded with improved respiratory function and regression of eye and skin symptoms. 3 weeks after admission the patient was transferred to the intensive care unit. Leukocyte count had increased to $80 \times 10^9/\text{L}$. A new bone marrow biopsy still showed leukemoid reaction but no signs of malignancy. Abdominal CT scan showed lymphadenopathy and moderate enlargement of the liver and spleen.

The lymphadenopathy on the neck advanced, but fine-needle aspirations from these glands showed no malignant cells. The patient ultimately developed multi-organ failure and died 23 days after admission.

At autopsy the spleen was enlarged (weight 1700 g) with several small infarcts. The lymph nodes were grossly normal. The lungs were consolidated but without overt tumor formation. In the left cerebral hemisphere a tumor measuring $4 \times 4.5 \times 5 \text{ cm}$ was identified and shown to be a protoplasmic astrocytoma. Spleen, lungs, brain, kidneys, heart and bone marrow were sampled for microscopic analysis. Lungs and spleen were diffusely infiltrated with medium-to-large tumor cells with moderate to abundant cytoplasm (Fig. 2). Focally, the background showed increased neutrophils. The Tumor cells expressed CD30, ALK (finely granular cytoplasmic pattern), CD4, CD2 (weak) and CD25. They failed to express CD3, CD5, CD8, CD20, CD79a and PAX5. Similar tumor cells were infiltrating the myocardium, kidneys, bone marrow and brain, including the astrocytoma, as solitary single cells (Fig. 3A). Vascular transsections often showed intravascular ALK-positive tumor cells among the neutrophils (Fig. 3B). A diagnosis of ALK-positive anaplastic large cell lymphoma of T-cell lineage was made. Concurrently, the results of the cytogenetic analysis, including spectral karyotyping, of the last ante mortem bone marrow aspiration showed t(2;17)(p23;q23) in 11 of 30 metaphases, including a subclone with an additional t(3,8)(p21;q24) in 2 metaphases. No t(9;22) was identified.

In the light of these findings, the two bone marrow biopsies, the clots from the two pleural fluid examinations and the skin biopsy were reviewed. By conventional H&E staining and Giemsa staining both bone marrow biopsies were still without morphologically identifiable tumor cells or lymphoid aggregates (Fig. 3C). However, immunohistochemical staining showed scattered single lymphoma cells positive for CD30 and ALK (Fig. 3D). Similarly, single tumor cells were identified by CD30 and ALK staining in the pleural fluids but not in the skin biopsy.

**DISCUSSION**

Primary systemic ALCL is mainly of T-cell lineage and characterized by large pleomorphic cells with abundant cytoplasm, expression of CD30 and anaplastic lymphoma kinase (ALK). Translocation t(2;5) is commonly found in primary systemic subtypes and along with other translocations associated with the ALK gene. In our patient a variant translocation was found (t(2;17)), which is observed in about 2–5% of patients with ALCL, giving rise to the particular granular ALK expression pattern. As opposed to the indolent and progressive cutaneous type, systemic ALCL is aggressive and often located in extranodal sites such as the lungs and liver (1, 2). The disease infrequently involves pe-
Fig. 2. Microscopic and immunophenotypic findings in the enlarged spleen. (A) The spleen shows a loose stroma with a fibrous quality. Larger atypical lymphoid cells are dispersed in the stroma, ×200. (B) The neoplastic cells strongly express CD30 with granular cytoplasmic and Golgi region pattern, ×200 (insert, ×630). (C) There is strong ALK staining of the lymphoma cells with a granular cytoplasmic pattern. There is no membranous or nuclear staining, ×200 (insert, ×1000). (D) The lymphoma cells are also strongly CD25 positive, ×200. (E) The large atypical tumor cells are variably CD4 positive, ×400. (F) There are a very small number of scattered CD79a-positive small B-lymphocytes, ×200.
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Fig. 3. (A) Myocardium section shows single cell infiltration of lymphoma cells (arrows) that is difficult to detect by conventional hematoxylin eosin staining, ×200. (B) In the same area, extra- (arrows) and intravascular (arrowheads) ALK-positive tumor cells become apparent by immunohistochemistry, ×200. (C) Hematoxylin eosin staining of the second bone marrow biopsy shows hypercellularity, ×200. (D) Occult tumor cells (arrows) can only be distinguished from immature hematopoietic cells by immunohistochemistry demonstrating ALK-positive cells, ×200.

Peripheral blood (3), but in our case the patient presented with massive neutrophil granulocytosis. In addition, several organs showed focal neutrophil infiltration in the absence of necrosis and infection, and thus resembled the so-called neutrophil-rich ALCL albeit with fewer infiltrating neutrophils than described in the original publication of this rare morphological ALCL variant (4).

The importance of immunophenotyping has been emphasized in the diagnosis of this rare but highly aggressive T-cell lymphoma, which may otherwise be misdiagnosed as an inflammatory disease (5). In the present case, malignant cells were not demonstrated by conventional pathological examination, which explains why immunophenotyping was performed late and diagnosis of ALCL was delayed. In a paper by Fraga et al. only 17% of ALCL patients were found to have bone marrow infiltration on conventional examination, but after immunohistochemical analysis for CD30, 40% of the patients had infiltration of the bone marrow (6). Thus, more than half the patients with bone marrow disease had occult tumor cells detectable only by immunohistochemistry.

Regarding the cause of the neutrophil-rich infiltrates, interleukin-8 has previously been sus-
pected of inducing neutrophil granulocytosis and neutrophil infiltration in lymphomas. However, Foss et al. (7) reported that only a few cells showed IL-8 expression in Hodgkin and non-Hodgkin lymphomas, and they proposed that other cytokines such as G-CSF and MG-CSF may be responsible for the neutrophil activation. In fact, a markedly elevated G-CSF has been observed in some ALCL patients (8) and has been proposed to be produced by the tumor cell line (9).

Studies by Reding et al. (10) showed that in 100 patients with extreme leukocytosis, defined as more than $25 \times 10^9/l$, 48% of the cases were attributed to infection and 13% to malignancy—mainly malignant melanomas, lymphomas and CML. The remaining 39% were attributed to various causes, such as glucocorticoid therapy, hemorrhage and G-CSF therapy. The treatment with glucocorticoid may have raised the neutrocyte count further but cannot explain the leukemoid reaction seen in the present case. Common infectious causes of leukemoid reactions are miliary tuberculosis, pneumonia, meningitis and abscesses. In our case, all cultures, microscopy and PCR were negative and antimicrobial therapy was without effect. We therefore conclude that the leukemoid reaction was caused by ALCL. Neutrophilia is not uncommon in neutrophil-rich ALCL (11, 12); however, presentation of ALCL with a leukemoid reaction—as in this report—is highly unusual, though it has been described casuistically (9, 13).

Neutrophil dermatosis (Sweet's syndrome) is defined as sudden onset of fever, leukocytosis and tender erythematous plaques showing neutrophil infiltrations. Sweet's syndrome is associated with leukemoid reactions and in 20–25% of the cases with hematological and non-hematological malignancies. Although the present patient had skin manifestations, biopsies from these lesions showed minimal neutrophil infiltrations.

In conclusion, the present case demonstrates that ALCL is an important differential diagnosis in patients with an unexplained leukemoid reaction. Immunohistochemistry and cytogenetics are important ancillary tools in the diagnosis of these patients as bone marrow infiltration often is too subtle to establish the diagnosis by conventional bone marrow examination. Thus, awareness of these clinical associations is of the utmost importance if clinicians and pathologists are to employ the relevant diagnostic tools.

REFERENCES
