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Letter to the Editor

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Sir, The WHO classification of tumors of haematopoietic and lymphoid tissues [1] describes the presence of Charcot–Leyden crystals (CLC) with or without necrotic bone marrow tissue in eosinophilic neoplastic conditions and tumors derived from Langerhans cells. This case report describes CLC and bone marrow necrosis in *NPM1*-positive acute myeloid leukemia (AML). As several case reports have been published describing CLC in AML without eosinophilia [2–6], a rare morphological finding of diagnostic relevance should be considered.

A 43-year-old male, with no medical history of note, was referred to the emergency department of our hospital because of thrombocytopenia. The week before, he had been walking in the Romanian mountains and suffered from increasing muscle aches and fatigue and had been feeling feverish. After returning home, he went to his general practitioner who prescribed a nonsteroidal anti-inflammatory drug, which relieved the muscle pain. Afterward, however, he developed petechiae.

When being physically examined, he appeared fit and was otherwise normal, except for petechiae in the mucosa of the mouth. Laboratory analysis showed a hemoglobin concentration of 12.6 mg/dL, 52×10^9/L platelets, and 21.4×10^9/L leukocytes. The differential count was 8% blasts, 2% myelocytes, 2% metamyelocytes, 6% band cells, 41% neutrophils, 33% lymphocytes and 8% monocytes. As 8% blasts were counted and dysplastic characteristics were seen in granulocytes and monocytes, bone marrow examination was performed.

Figure 1 shows images of the cytological review of peripheral blood and the aspirate sample. The microscopic evaluation of the bone marrow aspirate showed mainly necrotic bone marrow tissue in which numerous basophilic bipyramidally shaped crystals were visible that have previously been described as Charcot–Leyden crystals (CLC) [7]. Also, yellow pigment aggregates were observed. The bone marrow biopsy shown in Figure 2, also mainly showed necrotic hematopoietic tissue. A reactive background with plasma cells and macrophages was seen as well as a monotonic population of rather large blastic cells that were immunohistochemically negative for CD34 and positive for CD68. Expression of macrophage-restricted CD68 and absence of CD34 on blasts is frequently observed with *NPM1*-positive AML [1].

In peripheral blood, blasts were large with finely structured chromatin, discrete nucleoli, and frequently with irregular nuclear shape. Flowcytometric analysis showed that the blasts expressed markers of the myeloid lineage (CD45+, CD117+, CD13+, CD33+, cMPO+) were negative for CD34 and were also positive for the aberrant markers CD11c and CD7 (the latter being positive in about 30% of blasts). CD68 was not included into the flowcytometric analysis of the peripheral blood blasts. Cytogenetics did not provide additional information, and molecular diagnostics showed a prognostic favorable combination of negative *FLT3* and positive *NPM1*. Despite the fact that blasts could only be observed in peripheral blood with a relatively low count (8%), the diagnosis (*NPM1* mutated) AML was established. This conclusion was based on the deviant immunephenotype of the blasts, the monotonic population of blasts in the bone marrow biopsy and the mutation analysis. Formally, however, chronic myelomonocytic leukemia could not be excluded (monocytosis, fewer than 20% blasts, and dysplasia in multiple cell lines). After one cycle of chemotherapeutic treatment, complete remission was reached and no CLC or necrotic tissue was detected in the bone marrow aspirate and biopsy. He completed two additional chemotherapy cycles and was still in complete remission 5 months after presentation.

Charcot–Leyden crystals are a rare but known phenomenon in immunology. They solely consist of the enzyme lysophospholipase which is present in the granules of eosinophils and basophils [7]. It is assumed that the hydrophobic nature of the enzyme is responsible for the crystal formation. It is unknown what role the enzyme plays in the bone marrow tissue necrosis. The crystals are mainly found in body fluids and tissues in eosinophilic inflammatory reactions as in parasitic infections and allergic conditions (e.g., in sputum of asthma patients) but also in hematological malignancies associated with eosinophilia.

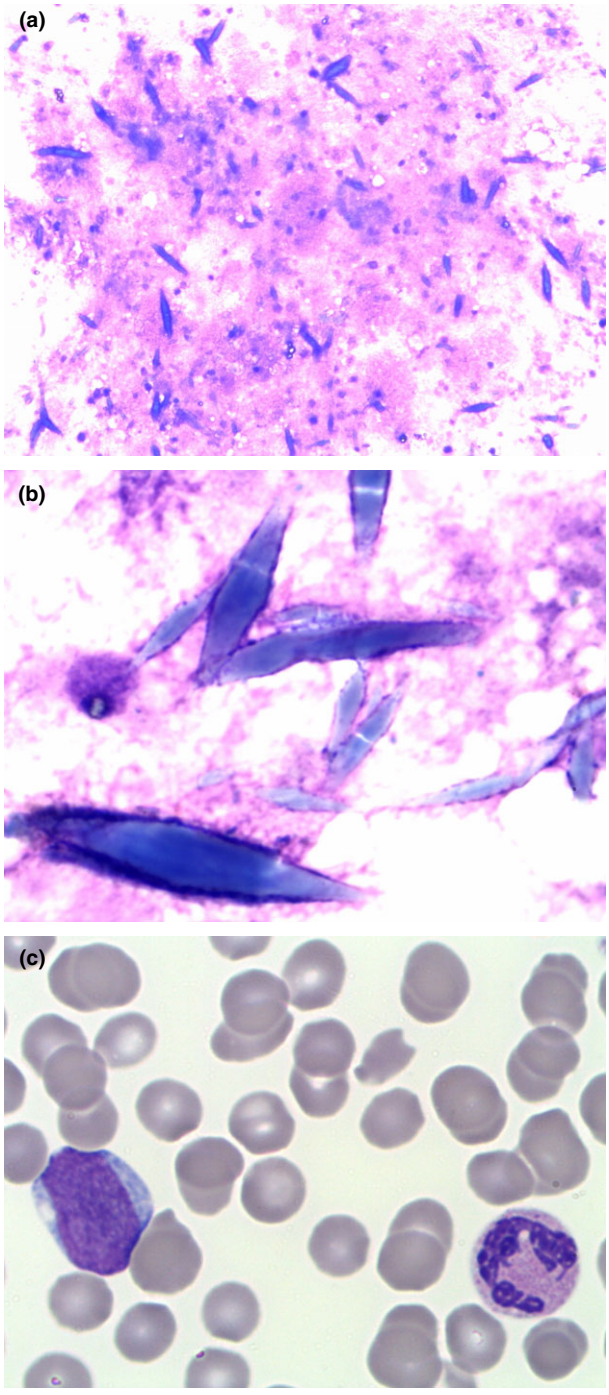

Figure 1. Bone marrow aspirate showing (a) necrotic bone marrow tissue and basophilic Charcot–Leyden crystals (MGG-stain, ×100), (b) bipyramidal Charcot–Leyden crystals (MGG-stain, ×1000), and (c) an image of a blast and a neutrophilic granulocyte in peripheral blood (MGG-stain, ×1000).

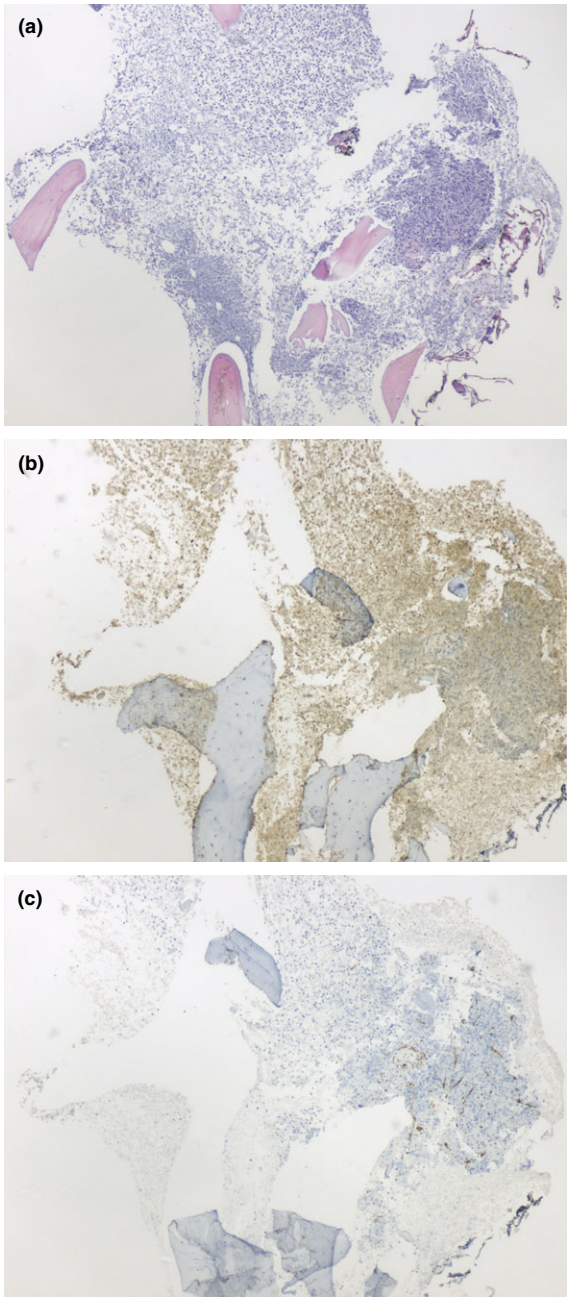

Figure 2. Bone marrow biopsy consisting of mainly necrotic hematopoietic tissue with blastic 'ghost cells' (a) that stain positive for CD68 (b) and are negative for CD34 (c).

The WHO described CLC in myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*, chronic eosinophilic leukemia not otherwise specified and tumors derived from

Langerhans cells [1]. We found one case report of MDS [8] and one case report of AML evolved from antecedent myelodysplastic/myeloproliferative neoplasm [9], both with prominent bone marrow eosinophilia. Also, one case of Hodgkin lymphoma with minor eosinophilia and CLC has been described [10]. In each of these cases of CLC with eosinophilia, presence of tissue necrosis was lacking.

In case of our patient, no eosinophilia was observed. Therefore, the observed characteristics of this case are not adequately described by the current WHO consensus document. To our knowledge, five case reports have been published previously describing bone marrow CLC in hematological malignancies without eosinophilia. Awluwalia *et al.* [2], Vermeersch *et al.* [3], Taylor *et al.* [4], and Manny *et al.* [5] described CLC in necrotic bone marrow of patients with AML. Radujkovic *et al.* [6] described a case of AML with the same immunophenotypical myeloid markers present, including the partial positivity for CD7. In each case, morphological examination was difficult because of the striking tissue necrosis in bone marrow. Review of the described case reports suggests that there might be two different phenomena. One is CLC associated with eosinophilic conditions, and the other is CLC associated with AML without eosinophilia but with tissue necrosis. As CLC are rarely observed, there is insufficient proof that these are separate hematological entities. However, taken the number of case reports in account that describe the combination of CLC and bone marrow necrosis in AML, pathologists and hematologists should be aware of this morphological finding, because AML diagnosis is often impeded by the bone marrow necrosis.

In conclusion, we present a patient with AML without evidence of eosinophilia who has Charcot–Leyden crystals in necrotic bone marrow tissue. The presence of bone marrow necrosis might be a specific feature of AML-associated CLC as opposed to eosinophilia-associated CLC. As previous case reports have made similar observations, the morphological recognition of CLC and bone marrow necrosis is of diagnostic relevance as AML diagnosis can be impeded.

Conflict of interest

The authors declare that they have no conflict of interest.

D. van de Kerkhof*, V. Scharnhorst*, C. J. R. Huysentruyt†, A. V. M. Brands-Nijenhuis‡, A. A. M. Ermens§

**Clinical Laboratory, Catharina Hospital, Eindhoven, The Netherlands*
†Laboratory for Pathology and Microbiology, PAMM, Eindhoven, The Netherlands
‡Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands
§Clinical Laboratory, Amphia Hospital, Breda, The Netherlands
E-mail: daan.vd.kerkhof@catharinaziekenhuis.nl

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