

UNDIFFERENTIATED GRANULOCYTIC SARCOMA: A CASE WITH EPIDURAL ONSET PRECEDING ACUTE PROMYELOCYTIC LEUKEMIA

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ABSTRACT

This study reports a case of granulocytic sarcoma that developed in the epidural zone 25 days before clinical evidence of an acute promyelocytic leukemia. The case presented the diagnostic difficulties that are common to all aleukemic granulocytic sarcomas. Moreover, it highlights the very rare association between granulocytic sarcoma and acute promyelocytic leukemia, which is far from being explained.

Key words: granulocytic sarcoma, acute promyelocytic leukemia, Ewing's sarcoma

Granulocytic sarcoma (GS) is a tumor composed of granulocytic precursor cells that originate in extramedullary sites. In most cases the tumor develops during acute myelogenous leukemia (AML).^{1,2} The onset of GS in healthy subjects without leukemia is very rare and only 160 cases have been described so far.¹⁻¹⁰

GS is associated with every cytologic FAB subclass, but is seldom found with acute promyelocytic leukemia (APL: M3).^{3-5,7-10}

We describe here a case of GS with epidural onset, diagnosed about 25 days before APL became hematologically and clinically evident.

Case report

R.A. is a 27-year-old male. On the 30th of July 1993, the patient experienced saddle hypoesthesia, acute urinary retention, and complete impairment of flexo-extension movements in the left foot. The next day he was hospitalized. Blood cell count was normal: Hb 12.5 g/dL, RBC $4 \times 10^{12}/L$, WBC $5.8 \times 10^9/L$ (with N 88%, E 1%, L 8% and M 3%), PTL $168 \times 10^9/L$. On August 1st he underwent surgery. During L3-L4 laminectomy, a lobulated bluish tumor sticking

to, but not infiltrating, the L4 body was removed. Histological analysis demonstrated a malignant small cell tumor, possibly an extraosseous Ewing's sarcoma.

Platelet count began to decrease on the 14th day after surgery and progressively dropped to $21 \times 10^9/L$ by the 24th day. WBC count fell to $2 \times 10^9/L$ by the 25th day. A bone marrow biopsy on the 26th day demonstrated myeloid cell line hyperplasia, mainly of the promyelocytic cell line, without neoplastic cells. On the 36th day, the WBC count suddenly increased, mostly due to a rise in myelocytes and hypergranulated promyelocytes (WBC $24.7 \times 10^9/L$ with N 21%, L 11%, M 2%, MMC 3%, MC 14%, PMC 47% and BL 2%). At the same time a pre-existing subclinical DIC worsened. Taken together, these developments suggested a diagnosis of acute promyelocytic leukemia (classic subtype). This diagnosis was confirmed by a bone marrow aspiration biopsy which demonstrated a high prevalence of promyelocytes with multiple peroxidase-positive Auer bodies; karyotypic analysis demonstrated a translocation $t(15;17)(q22;q11)$ in all 70 metaphases examined.

On the basis of these data, we reviewed the epidural tumor slides and performed further

immunohistochemical analysis to determine whether or not the tumoral cells were myeloid.

Lysozyme, peroxidase and CD43-positive stains suggested the epidural tumor be classified as a *malignant small cell tumor, possibly GS*. Specimens of the epidural mass showed extensive necrosis and diffuse, infiltrative growth of immature mononuclear *blastic* cells with no non-hematopoietic neoplastic cells. The neoplastic cells showed round nuclei with finely granular chromatin, small nucleoli, and eosinophilic granular PAS-positive cytoplasm. Nuclear pyknosis and atypical mitotic figures were frequent. The tumor cells presented fine peroxidase-positive cytoplasmic granules and showed intense reactivity, diffusely for lysozyme and focally for UCHL 1 and CD 45 RO.

The patient was therefore treated with 50 mg/day of all-trans-retinoic acid (ATRA), which resulted in a rapid improvement of the DIC. In contrast, 5 days later an acute retinoic acid syndrome began: high fever, pulmonary infiltrates, fluid retention, impaired cardiac output, and elevated WBC count ($44.1 \times 10^9/L$). Accordingly, in addition to ATRA, the patient was started on chemotherapy (CT) with the 3-7 schedule (doxorubicin 30 mg/sqm/day for 3 days and Ara-C 100 mg/sqm/b.i.d. for 7 days).

A rapid improvement in the syndromic symptoms was obtained, but both pericardial and pleural effusions were observed. The ATRA treatment was then stopped on the 20th day. Since the combined action of ATRA and CT had not obtained a complete remission (CR) (60% of both promyelocytes and myeloblasts were still present), a 2nd chemotherapy course of idarubicin as a single agent (12 mg/sqm/ b.i.d. on the 1st, 3rd, 5th and 7th days) was carried out 24 days after the end of the 1st course. CR was still not obtained and the same treatment was repeated two more times. CR, together with disappearance of both the neurologic symptoms and the translocation (15;17), was achieved only after the 4th chemotherapy course (i.e. the 171st day after surgery and the 293rd day after the onset of symptoms). On the 18th of March the patient began radiotherapy, in a cycle that totalled 36 Gy, on the epidural site of the GS.

He is currently (September 1994) in good

health and awaiting bone marrow transplantation.

Discussion

GS, which can be considered a variant of AML, is often more difficult to diagnose than AML. The problems related to its diagnosis as well as its prognosis depend on its clinical mode of appearance. Diagnosis is easy when GS is synchronous with AML, or when it appears either in previously treated AML or in a chronic myeloproliferative disease.¹ Diagnosis becomes problematic when GS precedes the clinical appearance of AML.^{1,2} Since there are very few typical cyto-histological patterns, more than 75% of GS are mistakenly diagnosed as other neoplasms, mainly as malignant lymphomas.^{1,6}

On the basis of the myeloid cell morphology observed on slides stained with both hematoxylin-eosin and May-Grünwald-Giemsa, we can distinguish three groups of GS.⁶

First group: well differentiated (WD). Myeloid differentiation is easily diagnosed, so the diagnosis is also simple.

Second group: poorly differentiated (PD). The majority of cells are immature, so morphology may at first suggest a diagnosis of non-Hodgkin large cell lymphoma (G, H according to W.F.).

Third group: undifferentiated (BL). Most of the cells are very immature, and the general pattern suggests either a lymphoblastic lymphoma or a non-hematopoietic neoplasm, above all Ewing's sarcoma.

The case presented herein belongs to the third group, which is the one that presents the greatest diagnostic difficulties.

It is worth highlighting some of the typical features of APL (between 6 and 15% of total AML) that further distinguish this from other FAB subclasses. The incidence of APL secondary to treatment is very rare (19 APL cases out of 1303 AML cases).¹¹ No cases of APL were found either in a series of newly diagnosed AML with trilinear dysplasia at onset, or in one of AML with clonal remission.^{12,13} These data suggest that the target of the leukemic event in APL is a precursor cell that differentiates towards a granulocytic-monocytic lineage. In contrast, in other

cytologic subclasses of myeloid leukemias the target cells are represented by the stem cells, which, since they are capable of multilinear differentiation, are able to undergo a clonal preleukemic phase with or without dysplastic patterns.

APL may present with unusual morphologic picture,¹⁴ but is seldom associated with GS. In hundreds of cases GS has been reported in association with various AML subclassess, but GS with APL is reported only 7 times, two of which were non leukemic patients.^{4,8}

It should be noted that in the present case there was a contrast between the highly anaplastic cyto-histologic patterns of the epidural mass and the more differentiated patterns of the marrow samples. This contrast could suggest that during leukemic evolution the neoplastic stem cell partially differentiates towards a granulocytic-monocytic series.

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