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Extramedullary Pleural Blast Crisis During Otherwise Chronic Phase in Chronic Granulocytic Leukaemia*

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Abstract—*A patient with Ph¹-positive chronic granulocytic leukaemia with extramedullary myeloblastic transformation in the pleural cavity is presented. The clonal origin of the blast cells obtained from the pleural fluid was confirmed by the presence of the Ph¹ chromosome. In addition, each cell had 4 extra chromosomes (+8, +21, +21, +mar) indicating independent clonal evolution.*

The patient survived for 6 months *after the occurrence of pleural relapse. The peripheral blood never showed transformation, but other systemic involvements of primitive myeloblasts were noted at autopsy.*

INTRODUCTION

THE OCCURRENCE of extramedullary blastosis in chronic granulocytic leukaemia (CGL) preceding the haematologic transformation is rarely encountered [1]. Most of the reported patients have had peripheral lymphadenopathy [1–4]. There are few reports of myeloblastic involvement in localisation such as breast, cerebrospinal fluid, bones, or other extramedullary sites, developing before the blood and marrow had predominantly been blastic [1, 5–11].

We present here an adult with Ph¹-positive CGL developing blastic crisis in the pleural cavity. This occurred while the bone marrow and peripheral blood remained in the chronic phase. The morphological, cytochemical, and cytogenetic characteristics of the blast cells obtained from the pleural fluid are described.

Case report

A male aged 63 years was diagnosed as having CGL in June 1973. At the time of diagnosis the spleen was greatly enlarged and all bone marrow metaphases were shown to have one Philadelphia chromosome. Busulfan therapy was started and blood counts as well as the spleen size became normal. In October 1974 the leucocyte count rose to 85.8×10^9/l with 11% myelocytes. Busulfan was changed to 6-mercaptopurine (150 mg/day) and a good control of the disease was achieved. In March 1975 leucocytosis reappeared (38.3×10^9/l with 25% myelocytes). Hydroxyurea was started (1500–500 mg/day) and the patient entered a stable 'remission'. Thereafter, the patient was on hydroxyurea, and peripheral blood counts stayed within normal limits. In January 1978 progressive tiredness and a dry cough appeared. The patient was admitted to hospital on 10 February 1978. The physical examination on admission revealed a pale elderly man in relatively good condition. The most significant pathological finding was a pleural effusion on the right. A pleural punction yielded 1200 ml of serous fluid. Cytological examination of the pleural fluid revealed a high number of blast cells (20×10^9/l). At the same time, there were no signs of transformation of CGL or even of any accelerated phase in the bone marrow or peripheral blood.

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Table 1. Cytological characteristics of blast cells in pleural fluid

Characteristics studied	Sample I 28.2.1978	Sample II 20.4.1978
Number of blasts (%)	90%	30%
Morphology (light microscopy)	Myeloblastic	Myeloblastic
Morphology (electron microscopy)	Not done	Blastic
Peroxidase [12]	1.5% positive	1.0% positive
Sudan black B [13]	N.D.	1.0% positive
Alkaline phosphatase [14]	0.5% positive	N.D.
Acid phosphatase [15]	N.D.	Few positive
Naphthol AS acetate esterase [16]	90% positive	N.D.
Alpha-naphthyl acetate esterase [17]	N.D.	Few positive
Periodic acid–Schiff [18]	N.D.	Few positive
Mitotic index	0.5%	N.D.
EAC-rosettes [19]	N.D.	Negative
E-rosettes [20]	N.D.	Negative
Karyotype [21] (7.3.1978)	50,XY,+8,+21,+21+mar[Ph^1;t(9;22)]	

The clinical course after the detection of the pleural blastosis is summarized in Fig. 1. During the local intrapleural cytostatic therapy the amount of pleural fluid diminished and its content of blasts gradually decreased but never reached zero. Serum protein electrophoresis, immunoglobulin levels, coagulation profile, serum urate, and the liver function tests were normal. ESR ranged from 19 to 80 mm/hr.

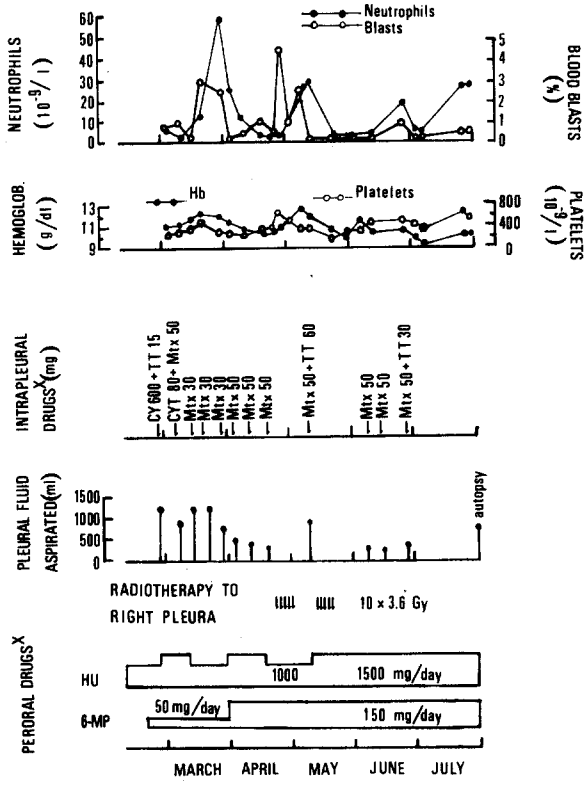

Fig. 1. Clinical course after onset of pleural blastosis in CGL. Abbreviations: CY=cyclophosphamide, CYT=cytosine arabinoside, HU=hydroxyurea, 6-MP=6-mercaptopurine, Mtx=methotrexate, and TT=thiotepa. 1 Gy=100 rad.

From 14 April 1978 the patient was treated as an out-patient. The last admission took place on 25 July when his condition had deteriorated significantly and he had fever. A chest X-ray showed the fluid in the right pleural cavity to be considerably increased. The peripheral blood picture was still clearly in the chronic phase (see Fig. 1). The fever did not disappear with penicillin and gentamycin. Death occurred on 30 July 1978, 6 months after the appearance of the extramedullary blast crisis.

Post-mortem examinations revealed heavy blastic infiltration in the pleura, lungs, liver sinusoids, spleen, and in the bone marrow. About half of the bone marrow cells were abnormal myeloblasts.

MATERIALS AND METHODS

A cytochemical characterization of pleural effusion cells was done twice. The following methods were adapted: peroxidase [12], Sudan black B [13], alkaline phosphatase [14], acid phosphatase [15], naphthol AS acetate esterase [16], acid alpha-naphthyl acetate esterase [17], and periodic acid–Schiff [18]. Cell surface markers (EAC- and E-rosettes) were analysed as described previously [19, 20]. The karyotyping of pleural blasts was performed by using a Giemsa-banding technique [21].

RESULTS

The cytological characteristics of the pleural blasts are given in Table 1. The blasts were poorly differentiated myeloid cells (Fig. 2). All 40 pleural mitoses studied had one

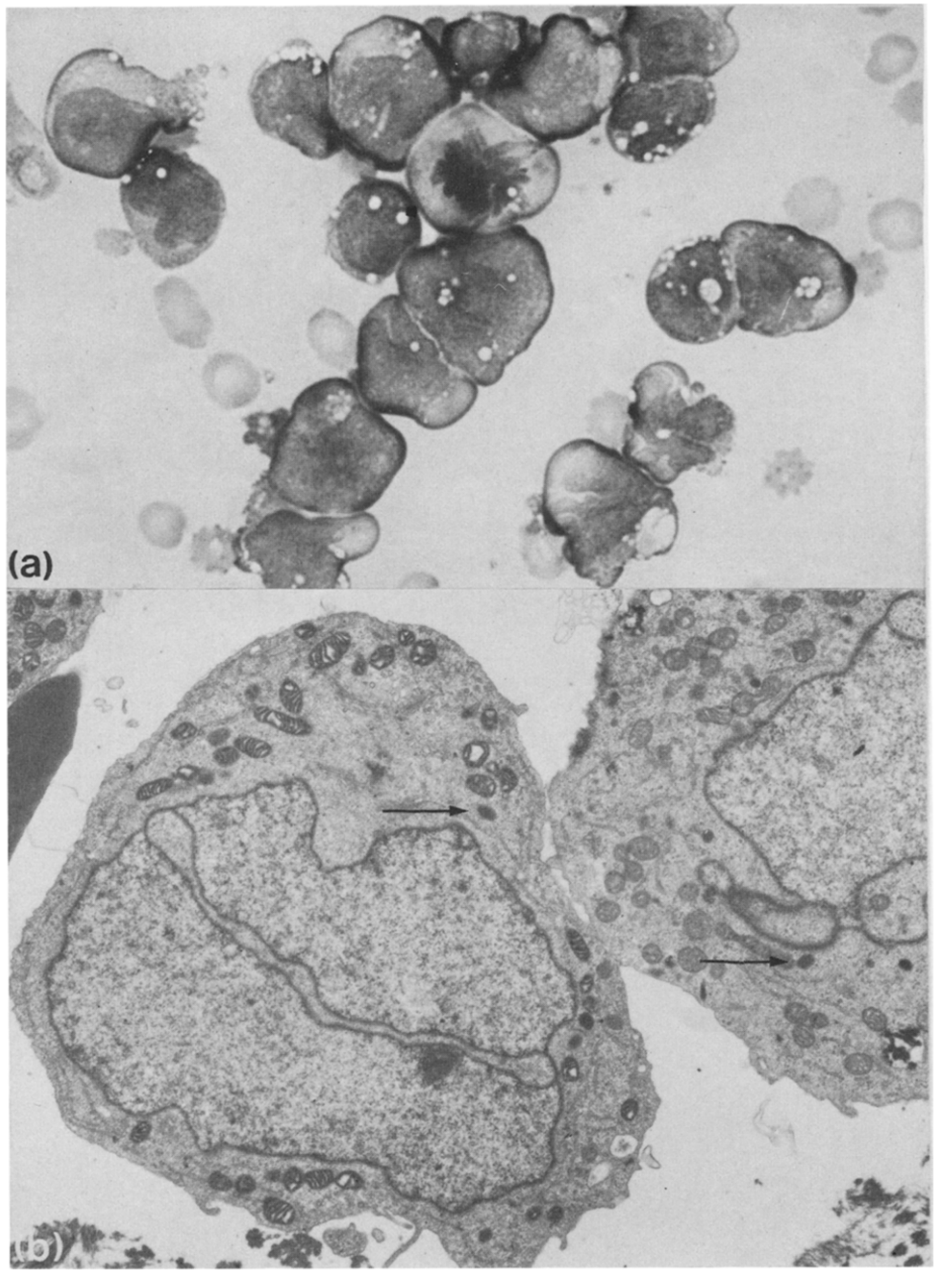

Fig. 2. Morphology of pleural effusion cells. (a) Light microscopy. Poorly differentiated myeloid blasts. MGG stain. × 850. *(b) An electron micrograph. The nuclear membrane is convoluted. Some profiles of rough endoplasmic reticulum, Golgi complex, mitochondria and granules (arrows) are seen in the cytoplasm. Uranyl acetate and lead citrate stain.* × 7200.

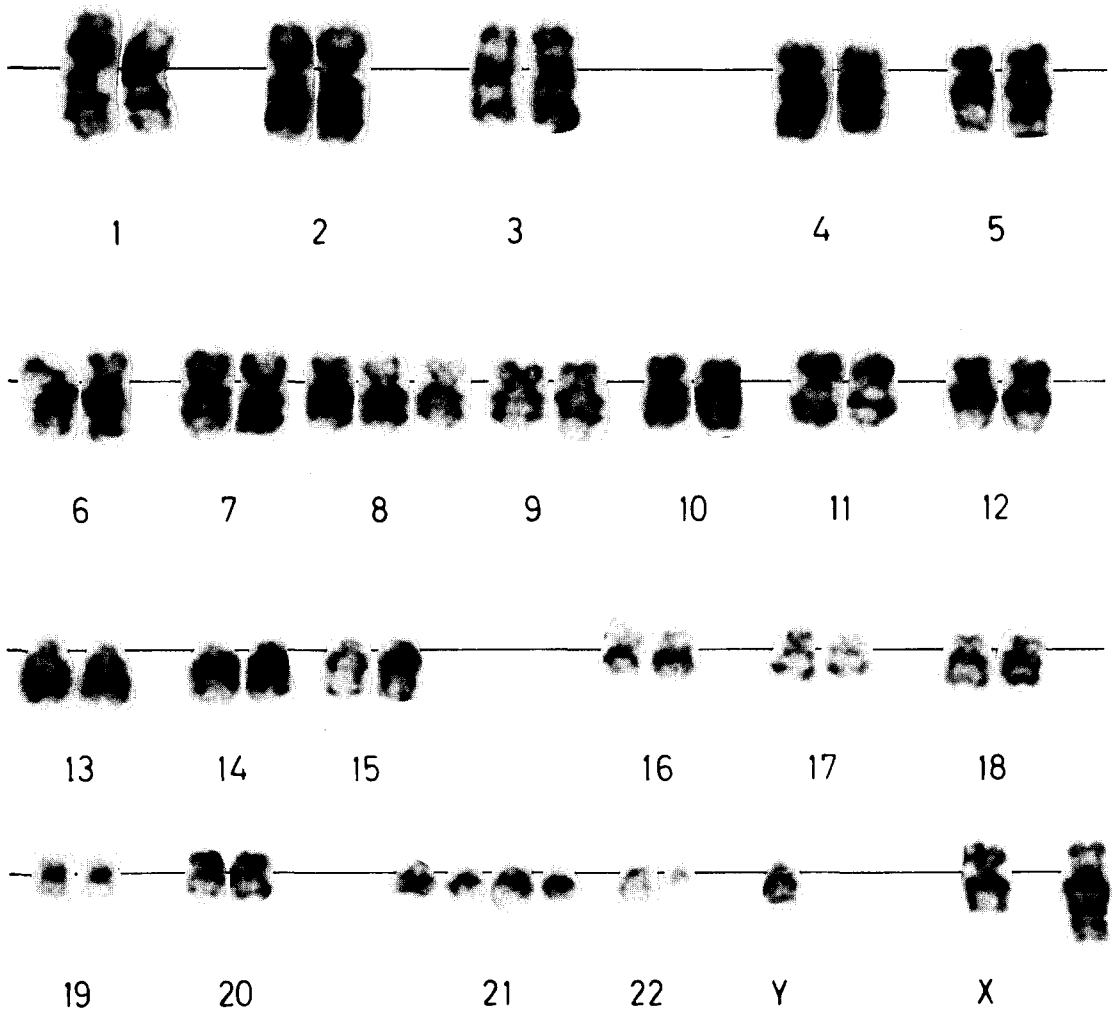

Fig. 3. Trypsin G-banded karyotype from a pleural effusion cell. Note a Philadelphia chromosome with the standard $t(9;22)$, *and 4 extra chromosomes,* $+8, +21, +21, +mar$. *The marker chromosome is at bottom right.*

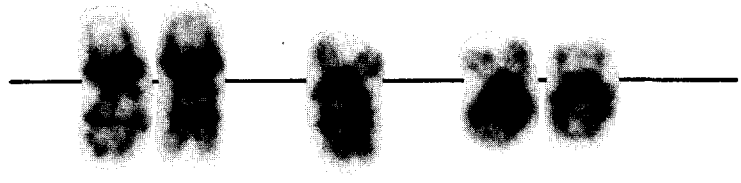

Fig. 4. Cut-out trypsin G-banded chromosomes 1 and 6 and the marker chromosome (middle) from a pleural effusion cell. The banding of the marker chromosome is consistent with the interpretation $6pter \rightarrow 6q21 :: 1q21 \rightarrow 1qter$.

Philadelphia chromosome that had arisen through the standard [9;22] translocation. In addition, each cell had four extra chromosomes, 50,XY,+8,+21,+21,+mar(Ph^1). This karyotype is shown in Fig. 3. The banding of the marker chromosome was consistent with a t(1;6)(q21;q21). According to this tentative interpretation, the marker chromosome was a 6pter→6q21::1q21→1qter (Fig. 4). That the disease was still in chronic phase in the bone marrow was ascertained cytogenetically and morphologically twice (7 March and 25 May 1978), the karyotype of all bone marrow metaphases being 46,XY(Ph^1) with the standard translocation on both occasions. The bone marrow morphology did not show any changes differing from the typical picture seen in the chronic phase of CGL. In the latter sample, some megaloblastic changes were recorded.

DISCUSSION

Blastic crisis is the most common cause of death in patients with CGL [22–25]. An extramedullary blast crisis complicated the course of the disease in 37% of the cases in a series of 73 patients with Ph^1-positive CGL [1]. Of the cases of extramedullary blast crisis in that series, 44% represented patients in whom the extramedullary lesion appeared prior to or simultaneously with the development of bone marrow transformation. On the other hand, there are only a few reported cases in which the extramedullary blastic transformation had significantly preceded the blastic phase of bone marrow or peripheral blood as in our case. Destructive bone lesions in CGL are encountered in a few cases [8–10]. The lesions appearing before the systemic transformation have been described as undifferentiated myeloid tumours, but no cytogenetic data about these tumour cells are available. Peripheral lymphadenopathy is sometimes the first of sign of relapse in CGL. IN one series [1] the soft tissue and nodal involvements preceded marrow transformation by up to 3 months. The clonal origin of blast cells occupying the lymph nodes before the marrow blastosis has been ascertained by the presence of the Philadelphia chromosome [1, 2, 4], and so has the clonal nature of the pleural blasts in the present case, too. In one patient Ph^1-positive myeloid blasts were detected in the cerebrospinal fluid about 3 months prior to the blastic transformation of the peripheral blood [6].

Blastic transformation of CGL is typically characterized by additional chromosomal abnormalities on top of the Philadelphia chromosome [26]. Extra chromosomes No. 8 are extremely common, and extra chromosomes No. 21 are not uncommon in this respect [27–30]. It is interesting that the marker chromosome consisted in part of the region 1q21→1qter, which is often known to occur in triplicate in malignant cells [31].

Cytogenetic characterization of extramedullary blasts has been reported only rarely. In the present study, the extramedullary clonal evolution with the acquisition of extra chromosomes in a previously Ph^1-positive cell line appears well documented. This type of proliferation has previously been shown to take place in lymph nodes [1], subcutaneous haematoma area [5], and spleen [32].

The true incidence of extramedullary relapses in CGL preceding the blastic crisis of bone marrow or peripheral blood is difficult to evaluate. Only the few cases where the extramedullary relapse readily causes symptoms (e.g., meningeal, subcutaneous and nodal involvements) are encountered. We do not know of any other case of extramedullary relapse in CGL where the crisis was first manifested as a pleural effusion. Leukaemic involvement of pleural fluid was detected in one patient, but this relapse occurred after the onset of systemic blast crisis [1].

Many features relating to the pathogenesis of extramedullary blast crisis are unknown. Careful study and reporting of informative cases may in time help throw light on open questions. In any event, cytogenetic examinations have proven useful in the study of malignant pleural effusions [33].

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