p230 does not always predict a mild clinical course in myeloid malignancies: e19a2 bcr/abl fusion transcript with additional chromosome abnormalities in a patient with acute monoblastic leukemia (M5a)

We report on a patient with an e19a2 positive acute myeloid leukemia (AML)-M5a resembling malignant histiocytosis in whom the diagnosis was made possible only by cytogenetic and molecular biology studies. The present case further suggests that an e19a2 transcript is not always associated with a mild clinical course.

In 1990 a rare Philadelphia (Ph) positive myeloproliferative disorder with mild splenomegaly, moderate leukocytosis with expansion of mature neutrophils, and thrombocytosis, marked by an e19a2 junction in the BCR/ABL hybrid gene transcript, was reported.[1] Since then an e19a2 junction has been observed in twelve patients with chronic myeloid leukemia (CML) either in chronic or in blastic phase,[2-8,10] but in only one case of acute myeloid leukemia (AML)[9] (Table 1). We describe the first e19a2 positive patient with a clinical presentation resembling malignant histiocytosis and with a diagnosis of AML-M5a finally made possible only by cytogenetics and molecular biology.

A 49-year old man, suffering from bone pain, intermittent fever and nocturnal sweating since January 1999, presented at our Institution in April 1999. On physical examination liver and spleen enlargement (4 and 1 cm) and a left arm nodular, round, hard and unpainful red lesion were noted. His blood count was: hemoglobin (Hb) 12.9 g/dL, white blood cells (WBC) 26.0×10⁹/L (differential: neutrophils 12%, eosinophils 2%, basophils 4%, lymphocytes 12%, monocytes 10%, agranulated blasts 60%), and platelets 107×10⁹/L. A bone marrow aspirate revealed 40%

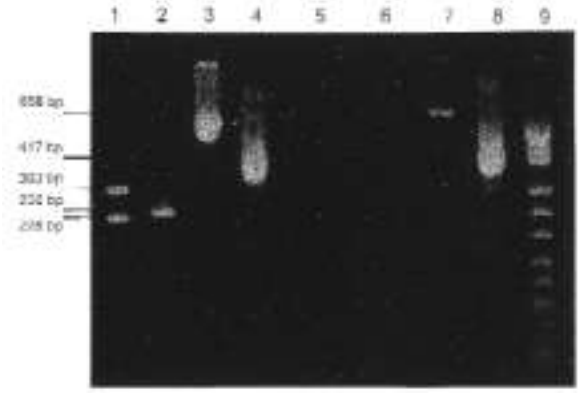

Figure 1. Agarose gel electrophoresis of reverse transcription-polymerase chain reaction products: a CML patient positive for both the 303bp b3a2 and the 228bp b2a2 transcripts (lane 1); an ALL patient positive for the 235bp e1a2 transcript (lane 2); 658bp and 417bp positive controls for first and second round e19a2 amplifications provided by Genenco (lane 3,4); our patient who tested negative for both b3a2 and b2a2 transcripts (lane 5), negative for e1a2 transcript (lane 6), positive for first round 658bp e19a2 transcript amplification (lane 7), positive for second round 417bp e19a2 transcript amplification (lane 8); DNA marker pUC18 MspI digest (Sigma), giving bands of 501bp, 489bp, 404bp, 353bp, 242bp, 190bp, 147bp, 110bp, 89bp, 67bp, 34bp and 26bp (lane 9).

Table 1. Clinical and hematologic characteristics of the 14 cases with e19a2 junction transcripts reported in the literature.

Case[ref]	Age/sex	Diagnosis	Splenomegaly	WBC (x10⁹/L)	Immature cells (%)	Neutrophils (%)	Platelets (x10⁹/L)	Karyotype	Blastic transformation	Survival* (mos.)
1[1]	76/F	CNL	Yes	28	N.A.	N.A.	1020	46,XX,Ph	N.A.	69
2[1]	62/F	CNL	Yes	16	N.A.	N.A.	870	46,XX,Ph	N.A.	36
3[2]	50/F	CML-AP	No	8	3	58	762	46,XY,Ph,i(17q)		29°
4[3]	65/F	CNL	No	58	1	87	160	46,XX,Ph	N.A.	36°
5[3]	41/M	CNL	No	43	2	88	191	46,XY,Ph	N.A.	≥131
6[3]	22/F	CNL	No	45	0	74	1240	46,XX,Ph	N.A.	≥96
7[4]	13/F	CML-CP	Yes	17	4	63	1442	46,XX,Ph	N.A.	12
8[5]	45/F	ET	No	15	2	72	1370	46,XX,Ph	N.A.	60
9[6]	70/M	CML-CP	Yes	68	39	44	373	46,XY,Ph	N.A.	N.A.
10[7]	24/F	CML-CP	Yes	203	N.A.	N.A.	689	46,XY,Ph	Yes	61
11[8]	29/F	CML-CP	Yes	205	N.A	N.A.	627	47,XX,Ph,Ph	Yes	8°
12[9]	49/M	AML-M2	Yes	87	45	6	75	49,XY,del(7)(p11),+8,Ph,i(17)(q10),+19,+Ph		3°
13[10]	78/M	CML-CP	No	38	7	65	1650	46,XY,Ph	Yes	7°
14[this case]	49/M	AML-M5	Yes	26	60	12	105	47,XY,+8,Ph/47,idem,i(17q)		13°

*Legenda. *= survival reported in the original manuscript; CNL=chronic neutrophilic leukemia; CML-CP=chronic myeloid leukemia chronic phase; CML-AP=chronic myeloid leukemia accelerated phase; ET=essential thrombocythemia; AML=acute myeloid leukemia; mo.=months; Ph=t(9;22)(q34;q11); N.A.=not available, °=dead.*

agranulated monocytoid-appearing elements with an elevated nucleus/cytoplasm ratio, an intensively basophilic cytoplasm, and 60% granulated elements with the same morphologic features. These blast cells were CD34, CD33, DR, CD4^{dim}, CD25, CD7, CD11b, CD11c, CD13, CD14, CD15 heavily positive and CD19, CD57, CD41a, myeloperoxidase-negative on immunophenotyping.

The karyotype was 47,XY,+8,t(9;22)(q34;q11)/48,idem,iso (17q), +der(22)t(9;22)(q34;q11). Reverse transcription polymerase chain reaction[1,3] failed to discover either the transcripts b2a2 and b3a2 or the transcript e1a2, but did identify an e19a2 transcript, already present after the first amplification step (Figure 1). A skeletal X-ray showed numerous lytic lesions involving the ribs, the right femur, the pelvis and the sacrum. A skin biopsy of the left arm lesion showed dermal infiltration by a CD15, myeloperoxidase-positive and alpha-naphthyl acetate esterase-negative blast cell population. A diagnosis of AML-M5a was made. Three courses of ICE, followed by two of HD-Ara-C 3 g/m^2 i.v. every twelve hours for two days were administered. In addition the patient received radiotherapy to the ribs (30 cGy) and the right femur (30 cGy). A complete hematologic, cytogenetic but not molecular remission, with complete disappearance of the skin lesion, was achieved after the first course of chemotherapy. After the second course of HD-Ara-C, however, the patient developed multiple skin and bone lesions that progressed despite two courses of idarubicin 12 mg/m^2 i.v. on the first day and Ara-C 500 mg/m^2 i.v. every twelve hours for two days. A lesion localized in the occipital region reached a diameter of 10cm and skull computerized tomography showed that it was infiltrating the dura and pressing on the brain. In March 2000 a new course of ICE, followed by radiotherapy to the neoplastic skin and bone localizations (26 cGy to the skull and 30 cGy each to the other localizations), causing a partial resolution of the infiltrations, was completed. From April to July the patient received three further courses of ICE. After the third he died of a pulmonary infection.

In conclusion our patient demonstrates that an e19a2 transcript does not always mean a mild clinical course as in very rare cases[9] it is associated with blastic transformation of an otherwise unrecognized chronic myeloproliferative disorder.

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