Clinical and Hematological Profile of Acute Megakaryoblastic Leukemia: A 2 Year Study

A. V. Jayasudha · Rekha A. Nair · Priya Mary Jacob ·
S. Renu · K. R. Anila · P. Sindhu Nair ·
T. Priya Kumari · P. Kusuma Kumary

Received: 28 November 2013 / Accepted: 22 May 2014 / Published online: 13 June 2014
© Indian Society of Haematology & Transfusion Medicine 2014

Abstract Acute megakaryoblastic leukemia is a rare subtype of acute myeloid leukemia with a characteristic morphologic and immunophenotypic profile. It has to be distinguished from other subtypes of acute myeloid leukemia as well as acute myeloid leukemia with t (1; 22) (p13;q13) and acute megakaryoblastic leukemia in Down Syndrome because of its poor prognosis. We studied ten cases diagnosed over a period of 2 years (from July 2011 to June 2013). All the ten cases were in the pediatric age group ranging from 4 months to 2 years. On morphology, pointers to the diagnosis were clustering of blasts, presence of cytoplasmic blebs and platelet budding. An additional interesting morphological feature observed in our study was nuclear blebs which were seen in nine cases. Diagnosis was confirmed in all cases by positive immunostaining for CD61. Two of the cases had an extremely rare clinical presentation as granulocytic sarcoma. Although rare, acute megakaryoblastic leukemia should be kept in mind especially in leukemia in infants.

Keywords Acute megakaryoblastic leukemia · Granulocytic sarcoma · Infants · Flowcytometry

Introduction

Acute megakaryoblastic leukemia is defined as an acute leukemia with 20 % or more blasts among which at least 50 % are of megakaryocytic lineage. This group excludes cases of acute myeloid leukemia with myelodysplasia related changes, acute myeloid leukemia with t (1; 22) (p13;q13), inv (3) (q21q26.2), t (3; 3) (q21;q26.2) and Down syndrome-related cases [1]. It is an uncommon disease comprising less than 5 % of cases of acute myeloid leukemia [1]. It may arise de novo or may be secondary to chemotherapy, or progress from myeloproliferative neoplasm and/or myelodysplastic syndrome [2–5].

Materials and Methods

The present study included ten cases diagnosed over a period of 2 years (from July 2011 to June 2013). One patient had acute megakaryoblastic leukemia associated with Down syndrome and was excluded from our study. Clinical presentation, hematological parameters like peripheral smear, bone marrow aspirate including trephine and immunoprofile of the cases were studied. Treatment and follow-up details were also noted.

Results

We analysed ten cases of acute megakaryoblastic leukemia diagnosed at our centre during a 2 year period from July 2011 to June 2013. Clinical profiles are summarized in Table 1. All the nine cases were within pediatric age group (4 months–2 years). Out of the ten cases, six cases were males. Hepatosplenomegaly was observed in five patients

A. V. Jayasudha · R. A. Nair (✉) · P. M. Jacob · S. Renu ·
K. R. Anila · P. Sindhu Nair
Department of Pathology, Regional Cancer Centre,
Thiruvananthapuram, India
e-mail: drrekhanair@gmail.com

T. Priya Kumari · P. Kusuma Kumary
Department of Pediatrics, Regional Cancer Centre,
Thiruvananthapuram, India

Table 1 Clinical features

Features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age/sex	1 year male	4 months female	4 months male	1 year male	5 months female	10 months female	2 years male	1 year female	1 year male	1 year male
Clinical feature	Fever	Fever	Fever loose stools	Fever	Multiple swelling—scalp proptosis	Fever	Fever	Fever	Bilateral swelling temporal region	Fever
Down syndrome	—	—	—	—	—	—	—	—	—	—
Hepatosplenomegaly	+	+	+	+	+	—	—	—	—	—
Lymphadenopathy	+	—	+	—	—	—	—	—	—	—

Table 2 Hematologic parameters

Features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Hb (g/dL)	7.7	4.3	10.1	6.2	5.5	4.5	8.5	6.2	5.2	10.4
WBC ($\times 10^9/L$)	59.6	23.5	16.1	14.8	12.1	22	26.7	26,000	15,500	9,700
Platelet ($\times 10^9/L$)	35	7	39	19	29	6	18	32,000	11,000	32,000

and lymphadenopathy in two patients. Hematologic profiles are summarized in Table 2. All the ten patients were anemic and thrombocytopenic. None of our cases presented with thrombocytosis. Leukocytosis was noted in five patients. Peripheral blood blast count was in the range of 1–58 %. Blasts in all cases showed cytoplasmic blebs and platelet budding. Distinct clustering of blasts was seen in two cases (Fig. 1). Another morphological feature observed in our study was the nuclear blebs which were observed in majority of cases. In one case, blasts showed circumferential nuclear blebs which resembled the steering wheel of a ship (Fig. 2a). Bone marrow aspirate smears were cellular in eight cases showing blasts ranging from 22 to 84 % with morphology similar to that seen in peripheral blood. Two cases yielded diluted marrow due to fibrosis. Diagnosis was confirmed by positive immunostaining for CD61 (surface and cytoplasmic) which was done in eight cases by flowcytometry in bone marrow aspirate (Fig. 2b), one case by flowcytometry in peripheral blood and in one case, by immunohistochemistry in cutaneous nodule biopsy. Immunoprofile of the tumour cells are summarized in Table 3. In contrast to the reported usual negativity of tumor cells for CD34 and CD45 in acute megakaryoblastic leukemia, six cases were CD34 positive and eight cases were CD45 positive.

Two of the nine cases (case 5 and case 9) were extremely unusual because of their clinical presentation as granulocytic sarcomas. Both cases were similar as they presented as soft tissue swelling in the head in infants with clinical diagnosis of metastasis possibly from neuroblastoma (Fig. 3). Case 5 was that of a 5 month old female

Fig. 1 Distinct clustering of blasts (Giemsa, $\times 200$). (case 10)

child who presented with multiple nodules in scalp and thigh and with proptosis. CT scan abdomen revealed absence of suprarenal mass. Fine needle aspiration cytology was done from cutaneous nodule in the scalp. Aspirate smears showed atypical cells in loosely cohesive clusters, vague rosetoid pattern and cords (Fig. 4a). Cytology smears were suggestive of malignant round cell neoplasm and was biopsied. Peripheral smear examination showed 18 % blasts many with cytoplasmic blebs. Patient was advised bone marrow studies including flowcytometry. Bone marrow aspirate yielded only blood. Bone marrow trephine was also not representative. Thus excision of scalp swelling was done and sent for histopathology. Histopathology examination showed tumour cells arranged singly

Fig. 2 a Blasts with nuclear blebs resembling ship's steering wheel, cytoplasmic blebs and platelet budding. *Inset* showing ship's steering wheel. (Giemsa, $\times 1,000$) (case 1), **b** CD61 positivity in flow cytometry (case 4)

Table 3 Immunophenotype of tumor cells

Case	Sample type	LCA	HLA-DR	CD34	Myeloid markers	Lymphoid markers
1	BMA	+	+	+	CD13, CD33, CD117, CD61	—
2	BMA	—	—	—	CD1107, CD61	—
3	BMA	+	—	+	CD13, CD33, CD61	—
4	BMA	+	—	+	CD33, CD117, CD 61, CD64	—
5	Cutaneous nodule	+	Not done	+	CD33, CD61, others—not done	Not done
6	BMA	+	—	+	CD117, CD61	CD19
7	BMA	+	—	—	CD13, CD117, CD61	—
8	BMA	+	+	—	CD13, CD61	CD10 CD2
9	PB	+	—	+	CD3, CD33, CD 61	—
10	BMA	—	—	+	CD 56, CD 117, CD 14, CD 33, CD 61	—

BMA bone marrow aspirate, PB peripheral blood, + positive, — negative

and in nests in a fibrous stroma (Fig. 4b). Immunohistochemistry showed positive staining of tumour cells for CD61 (Fig. 4c), CD34, CD45 and weak positivity for CD33. Other lymphoid and myeloid markers were negative.

Case 9 was that of a 1 year old male child who presented with bilateral swelling in temporal region and right periorbital region. CT scan abdomen showed absence of suprarenal mass. Fine needle aspiration cytology was done from swelling in temporal region and was suggestive of leukemia/lymphoma (Fig. 4d) and patient was advised hematological workup including flow cytometry. Peripheral smear examination showed 24 % blasts. Bone marrow

aspirate smears were diluted with blood and showed only 14 % blasts. Flowcytometry was done in peripheral blood and tumor cells were positive for CD34, CD45, CD13, CD33 and CD61 and negative for other myeloid and lymphoid markers.

On follow up, five patients did not take treatment and were lost to follow up. One patient succumbed to the disease. Four patients who had opted for treatment were treated according to the institutional protocol with cytosine arabinoside and daunorubicin. Three patients had persistent disease after induction chemotherapy and were advised palliation. One patient is currently on treatment.

Fig. 3 Soft tissue swelling in the head (case 5, case 9)

Discussion

Acute megakaryoblastic leukemia is a rare subtype of acute leukemia accounting for 7–10 % of childhood acute myeloid leukemia and 1–2 % of adult acute myeloid leukemia [6]. It is difficult to diagnose this variant solely on the basis of morphology. However, presence of clustering of blasts, cytoplasmic blebs and platelet budding is useful in arriving

at the diagnosis [1]. In our study, these findings were present in majority of the cases thus emphasizing their importance. Clustering of blasts was so obvious in two cases that it could be misdiagnosed as metastatic neuroblastoma. An interesting morphological feature observed in our study was the nuclear blebs which were observed in majority of cases. In one case, the blasts showed circumferential nuclear blebs which resembled the steering wheel of a ship. Bone marrow fibrosis if present is a very important feature and is seen in a high proportion of cases. In our study, bone marrow biopsy was available only in one case which showed fibrosis. Two of the nine cases had an extremely unusual presentation as granulocytic sarcoma. Granulocytic sarcomas of megakaryoblastic lineage are extremely uncommon. Our search of literature revealed three cases of granulocytic sarcomas of megakaryoblastic lineage. Two cases represented disease progression from chronic myeloproliferative neoplasm and one case was a granulocytic sarcoma in an infant without systemic manifestations of leukemia [4–6]. Diagnosis was confirmed in all cases by positive immunostaining of tumor cells for CD61 by flowcytometry or immunohistochemistry. Most flowcytometry panels for acute leukemia do not use CD61 antibody in their first panel. So it is important not to overlook the characteristic morphologic findings so that we

Fig. 4 **a** Atypical cells in loosely cohesive clusters and in vague rosetoid pattern (pap, $\times 1,000$) (case 5), **b** Tumor cells singly and in nests in fibrous stroma (H and E, $\times 400$) (case 5), **c** CD61 positivity of

tumor cells (IHC, $\times 400$) (case 5), **d** cytology smear showing atypical cells with scanty cytoplasm and immature chromatin (Giemsa $\times 1,000$) (case 9)

will include the CD61 antibody in the second panel. Such cases can be misdiagnosed as acute undifferentiated leukemia or acute myeloid leukemia with minimal differentiation. Cytoplasmic expression of CD61 is more specific and sensitive than surface staining because possible adherence of platelets to blasts may be misinterpreted as positive staining by flowcytometry [1]. Acute megakaryoblastic leukemias are often negative for CD34 and CD45 [1]. In our study seven cases were CD34 positive and eight cases were CD45 positive. Cytogenetic studies should be done in acute megakaryoblastic leukemia to exclude myeloid leukemia associated with Down syndrome and AML with t (1; 22), (p13;q13), inv (3) (q21q26.2), t (3; 3) (q21;q26.2) which was not done in our cases as cytogenetic studies were not available [1]. A review of literature revealed a single case series from India by Sharma et al. in which they have studied five cases over a period of 10 years [7]. Ours is the largest case series reported from India.

To conclude, acute megakaryoblastic leukemia, although rare, should be excluded especially in infant leukemias. Clustering of blasts characteristic of acute megakaryoblastic leukemias can be mistaken for metastasis from other small round cell neoplasms like neuroblastoma, especially when it presents in infants as granulocytic sarcoma, as seen in two of our cases. The clinical picture, other characteristic morphologic findings, together with

positive immunostaining for CD61 and cytogenetics will help us to arrive at an accurate diagnosis.

References

1. Arber DA, Brunning RD, Orazi A et al (2008) Acute myeloid leukaemia, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al (eds) WHO classification of tumors of haematopoietic and lymphoid tissues, 4th edn. International Agency for Research on Cancer, Lyon, pp 136–137
2. Pullarkat ST, Vardiman JW, Slovak ML et al (2008) Megakaryoblastic blast crisis as a presenting manifestation of chronic myeloid leukemia. *Leuk Res* 32:1770–1775
3. Miyoshi Y, Okada S, Takizawa Y et al (1991) Acute megakaryoblastic leukemia developing 11 years after diagnosis of essential thrombocythemia. *Rinshoketsueki* 32:868–873
4. Hirose Y, Manaki Y, Shimoyama K et al (2001) Granulocytic sarcomas of megakaryoblastic differentiation in the lymphnode terminating as acute megakaryoblastic leukaemia in a case of chronic idiopathic myelofibrosis persisting for 16 years. *Eur J Haematol* 67:194–198
5. Chan AC, Kwong YL, Lam CC (1996) Granulocytic sarcoma of megakaryoblastic differentiation complicating chronic idiopathic myelofibrosis. *Hum Pathol* 27:417–420
6. Kaufman BA, Jones L, Zutter MM et al (1993) Megakaryoblastic leukemia presenting as a temporal bone granulocytic sarcoma. Case report. *J Neurosurg* 79:128–131
7. Sharma S, Nangia A, Jain Malhotra S et al (2009) Clinico-haematological profile of acute megakaryoblastic leukaemia: report of five cases. *Adv Hematol* 2009:461912. doi:[10.1155/2009/461912](https://doi.org/10.1155/2009/461912)