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Case Report OMICS International

Lymphoid aggregates in Acute Myeloid Leukemia: A case report of four cases

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Abstract

Reactive Lymphoid aggregates (LA) in association with acute myeloid leukemia is an uncommon finding. We describe four cases of acute myeloid leukemia (AML) that showed lymphoid aggregates in the bone marrow biopsy. Methods and results: Detailed clinical, laboratory data and bone marrow biopsy findings were evaluated in all four cases of AML, showing LA in bone marrow biopsy. On immunohistochemistry, CD20 and CD3 positivity was observed with variable intensities and patterns.

Introduction

Reactive lymphoid aggregates (LA) in the bone marrow (BM) are relatively uncommon finding (1-2%) although their incidence increases with age [1]. The pathophysiological implication of LA in BM is not well understood. Reactive LA in the bone marrow has been reported in a variety of disorders like infection, inflammation, haemolysis, autoimmune diseases and also in hematopoietic clonal disorders such as chronic myeloproliferative disorders and MDS. They are predominantly composed of small well-differentiated lymphocytes admixed with varying numbers of plasma cells, histiocytes, mast cells, eosinophils and occasional larger lymphocytes [2].

Reactive LAs are typically small, are relatively uniform in size, have a distinct border, and have a non-paratrabecular location. They usually comprise of a mixture of B and T cells in distributed in various patterns which can be demonstrated immunohistochemically [1]. Presence of lymphoid aggregates is rather unusual and we have come across only one study where 2 cases of acute myeloid leukemia (AML) had this aggregates [1]. We here describe four cases of AML with lymphoid aggregates in BM biopsy.

Case Reports

Case 1: A 29-year-old male presented with persistent high grade fever for 3 months, cough and dyspnea on exertion for one month. Ultrasound abdomen showed mild hepatomegaly. His peripheral blood examination showed bicytopenia: TLC 1.4 × 10^9/l, Hb 79 g/l, platelet count 168 × 10^9/l and 5% blasts on differential count. B M aspirate showed 80% blasts with MPO positivity. On flowcytometry the blasts were positive for CD33, CD13, CD4 and HLADR (strong), while negative for CD34 along with other B and T cell markers. Thus a diagnosis of AML was made.

Case 2: An 18-year-old boy presented with complaints of high grade fever, cough and weakness for six months. On examination the patient had severe pallor with a single right axillary lymph node measuring 1 cm. There was no organomegaly. Hematological findings: Hb 28 g/l, TLC 4.4 × 10^9/l, platelet count 13 × 10^9/l and 25% blasts on differential count. BM aspirate showed 60% MPO positive blasts .On flowcytometry the blasts showed positivity for CD34, CD38, CD13, CD33, CD117, CD19(dim), HLA-DR, cMPO and were negative for other B and T cell markers. Thus a diagnosis of AML with aberrant expression of CD19 was made.

Case 3: A 50 year old male presented with fever, weakness, anorexia and vomiting for 10 days. On physical examination the patient was anemic with no peripheral lymphadenopathy or organomegaly. Hematological investigations: Hb 48 g/l, TLC 21 × 10^9/l, platelet count 300 × 10^9/l and 80% blasts on differential count. Hypercellular bone marrow aspirates revealed 85% MPO positive blasts with high nucleocytoplasmic ratio, round nuclei, fine chromatin, prominent nucleoli and small amount of granular cytoplasm and Auer rods. A diagnosis of AML was made. Flowcytometric immunophenotyping could not be done due to financial constraints.

Case 4: A 16-year-old boy presented with episodes of low grade fever, fatigue and bleeding tendencies for 10 days. Physical examination revealed multiple ecchymotic patches over left arm. His systemic examination findings were normal with no significant lymphadenopathy or organomegaly. Hematological investigations: hemoglobin 96 g/l, total leukocyte count 2.3 × 10^9/l, platelet count 22 × 10^9/l and 15% atypical promyelocytes on differential count. Coagulation studies showed mildly increased Prothrombin time (15.7 sec, C=12.1 sec), normal activated partial thromboplastin time and positive D-dimer test. BM examination revealed proliferation of atypical promyelocytes (~80%) with Faggot cells and intense MPO positivity. Flow cytometric analysis showed abnormal promyelocytes were positive for cMPO, CD13, CD33, CD117(dim), CD64(dim) and negative for CD34, HLA-DR, CD11b, cCD79a, CD19, CD4, CD7, and cCD3. Thus a diagnosis of hyper granular–APML was made. PML RAR translocation was positive by RT PCR. The clinico-pathological findings in all four cases are summarized in Table 1. None of the patients had any other associated chronic disorders, infectious or neoplastic pathology.

	Case 1	Case 2	Case 3	Case 4
Age/sex	29 years, male	18 years, male	50 years, male	16 years, male
Clinical history	Persistent high grade fever, cough and dyspnea for 3 months	High grade fever, cough and weakness for 6 months	Fever, weakness, anorexia and vomiting for 10 days	Low grade fever, fatigue and bleeding tendencies for 10 days

Physical examination	Mild hepatomegaly	Severe pallor with a single right axillary lymph node(1 cm)	Severe pallor	Multiple ecchymotic patches over left arm
Hemogram	TLC 1.4x10^9/l, Hb 79 g/l, platelet count 168 × 10^9/ l and 5% blasts on differential count	TLC 4.4 x 10^9/l, Hb 28 g/l, platelet count 13 × 10^9/l and 25% blasts on differential count.	TLC 21 × 10^9/l, Hb 48 g/dl, platelet count 300 × 10^9/l and 80% blasts on differential count	TLC 2.3 × 10^9/l, Hb 96 g/l, platelet count 22 × 10^9/l and 15% atypical promyelocytes on differential count. Increased prothrombin time and positive D-dimer test.
Bone marrow aspiration	80% myeloid blasts	60% myeloid blasts	80% myeloid blasts. Auer rods seen	Atypical promyelocytes 80% with Faggot cells
Cytochemistry	MPO positive	MPO positive	MPO positive	MPO positive
Flowcytometry	Positive for CD33, CD13, CD4 and HLADR (strong). Negative for CD34 along with other B and T cell markers	Positive for CD34, CD38, CD13, CD33, CD117, CD19(dim), HLA-DR, cMPO and negative for other B and T cell markers	Could not be done	Positive for cMPO, CD13, CD33, CD117 (dim), CD64 (dim) and negative for CD34, HLA-DR, CD11b, cCD79a, CD19, CD4, CD7, and cCD3. (PML RAR translocation was positive by RT PCR)

Table 1: Clinico-pathological findings of all four cases.

The trephine biopsy and immunohistochemical findings were as follows; Case 1: Hypercellular BM biopsy showed proliferation of medium sized blasts with markedly reduced normal hematopoietic elements. Three lymphoid aggregates comprising of small sized lymphocytes along with germinal center were present in inter-trabecular location. On immunohistochemistry (IHC) CD20 positive cells were present in center surrounded by CD3 positive cells at the periphery. Case2: Hypercellular BM biopsy showed proliferation of blasts with reduced normal hematopoietic elements. Two lymphoid aggregates consisting small mature lymphocytes in non-paratrabecular region were also seen. These LA had intensely positive core of CD3 positive cells surrounded by CD20 positive cells. Case 3: Hypercellular bone marrow biopsy showed marked proliferation of blasts with markedly reduced normal hematopoietic elements. Two small lymphoid aggregates comprising of small lymphocytes with few interspersed plasma cells were present in central inter-trabecular area. IHC showed central core of CD3 surrounded by CD20 positive cells Case 4: Hypercellular BM biopsy showed proliferation of atypical promyelocytes with reduced normal hematopoietic elements. Two tiny lymphoid aggregates, comprising of small lymphocytes admixed with few plasma cells and eosinophils were also seen. IHC showed mixed distribution of CD3+ and CD 20+ cells with predominance of CD3+ cells. The immunohistochemical findings are shown in Figure 1.

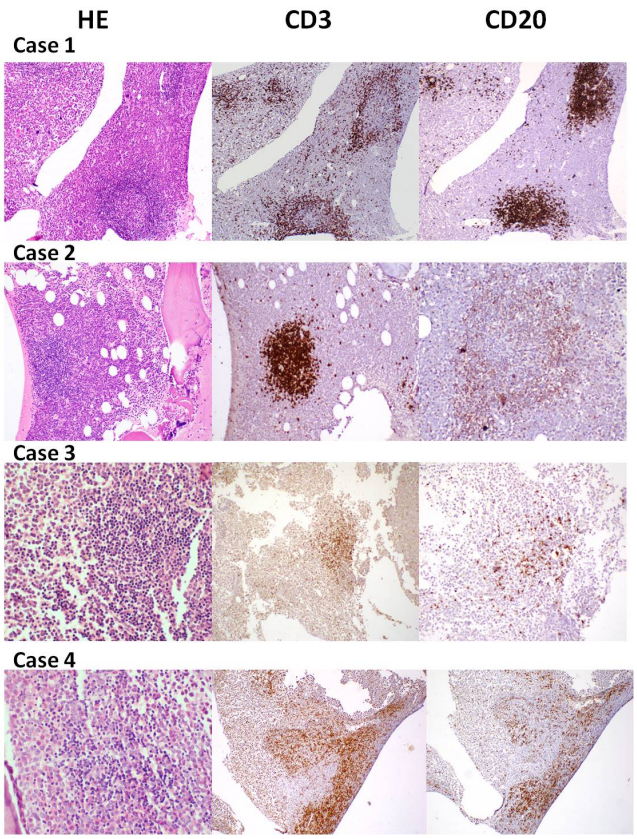

Figure 1: The trephine biopsy and immunohistochemical results.

The further course in first three patients could not be evaluated as they were not treated in our hospital and lost to follow-up. The fourth patient was started on ATRA + ATO protocol along with platelet and fresh frozen plasma support. Later on he developed ATRA syndrome which was successfully managed by dexamethasone. After six weeks of induction therapy patient was stable and in remission.

Discussion

Lymphoid aggregates are commonly seen in association with infections, chronic inflammatory conditions, autoimmune disorders and clonal hematopoietic disorders like myelodysplastic syndrome, lymphoproliferative and myeloproliferative disorders [2]. Thiele et al. [3] in a study of 18,000 BM biopsies found reactive lymphoid aggregates in 352 cases which included cases of CML, MDS but none of their case was associated with AML. The incidence of lymphoid aggregates in association with MDS varies from about 10-25% [4,5], however only two cases of AML with LA in bone marrow biopsy have been reported [1].

Various distribution patterns have been described in literature which includes predominantly T cells or B cells, mixture of B and T cells, core of B cells surrounded by T cells or a core of T cells surrounded by B cells. A mixture of T and B cells and predominantly T cells is most common pattern in seen in reactive process [1]. When

aggregates exhibit a predominance of T cells, consist of a central core of T cells surrounded by a rim of B cells, or have a mixed distribution of B and T cells, they are more likely to be benign. The likelihood of malignancy is increased when aggregates show a predominance of B cells or consist of a central core of B cells surrounded by a rim of T cells [1]. Two of our cases (Cases 2 and 3) showed a core of T cells surrounded by B cells. One of our cases (Case 1) had prominent germinal centers which were composed of B cells surrounded by a rim of T cells. The fourth cases showed a mixed distribution of both CD3 and CD20 positive cells with predominance of T cells. In our study, LA showed morphologic features of benign nodules, although in one case they were large which was further supported by immunohistochemistry.

The pathophysiology of reactive LA in MDS has been attributed to immunological abnormalities leading to cytokine dysregulation and persistent immune stimulation [6,7]. The altered BM microenvironment leads to increased bone marrow reticulin representing a damaged hematopoietic stroma. Reactive LA is more commonly seen in MDS with fibrotic marrow supporting the above hypothesis. However, none of our patient showed increased reticulin in BM biopsy indicating some other pathophysiologic mechanism.

The other possibility is could this phenomenon be similar to Tumor infiltrating lymphocytes (TIL) in solid tumors? TIL are often found in tumors, presumably reflecting an immune response against the tumor and appear to bestow survival benefits on the host when present in situ as large aggregates of activated T and B cells [8].

The two interesting observations of our study are, that we have come across these lymphoid aggregates in AML is a recent phenomenon, as all the four cases were diagnosed in last two years and three out of four patients belonged to a younger age group. Thus, possibility of changing immune response to various environmental factors may also be surmised. However the exact significance of our findings needs further workup.

There is paucity of literature on the presence of reactive lymphoid aggregates in association with AML. Their exact pathophysiology and biological significance is unknown, however similar mechanisms as mentioned in MDS could possibly explain their occurrence.

Conclusion

The exact pathophysiology and biological significance of reactive lymphoid aggregates in AML is unknown and need further workup.

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