International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Case Report

Small Cell Variant of Anaplastic Large Cell Lymphoma with Granulomatous Reaction- A Relook at Cytology

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Received: 17/05//2012 *Revised: 01/06/2012* *Accepted: 02/06/2012*

ABSTRACT

Granulomatous reaction occurs in several neoplastic processes including lymphoma. Many a times granulomas are extensive and mask the malignant cells, rendering the diagnosis difficult, more so at cytology. We report a case of five year old male child who presented with left sided axillary lymphadenopathy. Fine needle aspiration cytology (FNAC) showed features of granulomatous lymphadenitis. Patient was started on antibiotics, but was lost for follow up. However he came back after 4 months with right axillary lymphadenopathy. FNAC showed small atypical lymphoid cells, epitheliod cell clusters and rare "hallmark cells". Excision of right axillary lymph node was done. Histopathology and ancillary techniques favoured the diagnosis of small cell variant of anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALCL) with granulomatous reaction. On reviewing, FNAC slides of left axillary lymph node showed presence of atypical small lymphoid cells which were masked by granulomas along with rare "hallmark" cells. The present case illustrates the cytology findings of a rare case of small cell variant of ALCL and its association with granulomatous reaction.

Key words: Granulomas, anaplastic large cell lymphoma, small cell variant, fine needle aspiration cytology, hallmark cells

INTRODUCTION

Hodgkin's and non-Hodgkin's lymphomas (NHL) can sometimes show granulomatous reaction. At times these reactions may mask the neoplastic cells rendering diagnosis difficult, especially at cytology. Granulomatous reaction is not very common in ALCL. [1] Small cell variant of ALCL is an uncommon variant occurring frequently in young males and associated with aggressive behaviour. It differs from common type of ALCL by predominance of small cells and scarcity of typical "hallmark

cells". In addition, presence of granulomatous reaction adds to the diagnostic dilemma which leads to an erroneous diagnosis of an inflammatory lesion at cytology. [2] Histopathology and ancillary techniques are must to resolve the diagnostic problem. To our knowledge this is the first case report of small cell ALCL with granulomatous reaction.

CASE DETAILS

A five year old child presented to the surgery OPD with left axillary lymphadenopathy of two months duration. There was no history of fever, cough or weight loss. On examination there was no hepatosplenomegaly or lymphadenopathy at other sites. FNAC of left axillary lymph node showed cellular smears comprising of predominance of small lymphocytes along with few plasma cells, neutrophils, occasional eosinophils and plenty of epitheliod cells in clusters. (Figure 1) There was no evidence of caseation necrosis and acid fast stain for tubercle bacilli was negative. A diagnosis of granulomatous lymphadenitis was made. Patient was started on antibiotics but was lost for follow up. Four months later he returned with right axillary lymphadenopathy.

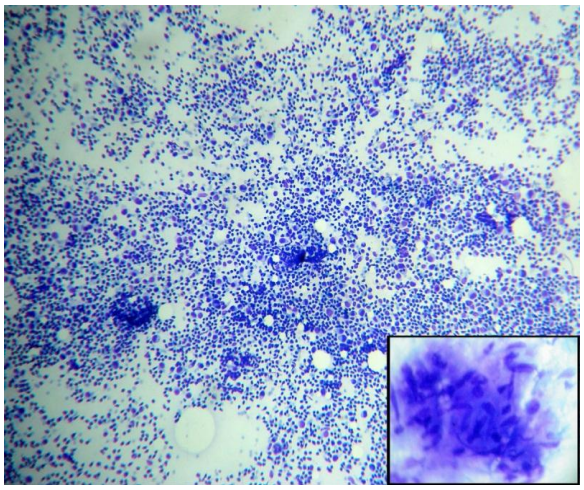

Figure 1: Cytology smear showing small lymphocytes with occasional neutrophils with epitheliod cell clusters in inset. (MGG × 100)

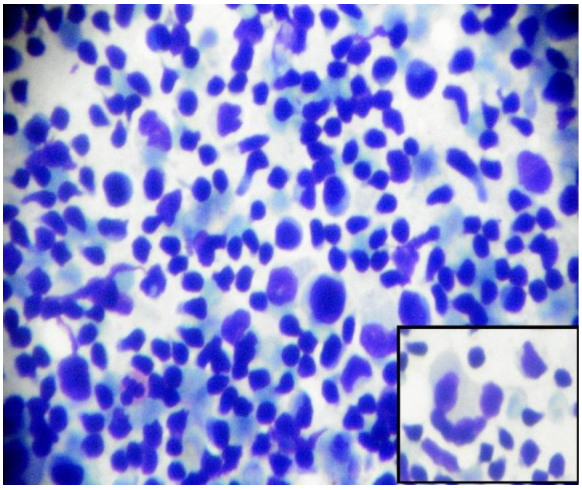

Figure 2: Cytology smears depicting atypical small lymphoid cells with characteristic "hallmark cells" in inset. (MGG × 400)

Fine needle aspiration cytology:

FNAC of right axillary lymph node showed predominance of small lymphoid cells with clusters of epitheliod cells, scattered neutrophils and eosinophils. Lymphoid cells were small, with irregular, cleaved nuclear membrane, coarse chromatin and prominent nucleoli. (Figure 2) Careful search revealed typical "hallmark cells" with horse shoe shaped nuclei. (Inset in Figure 2) A diagnosis of NHL with a possibility of small cell variant of ALCL with granulomatous reaction was suggested. Peripheral blood smear did not reveal any atypical lymphoid cells.

Histopathology:

Histopathology of right axillary lymph node showed partial effacement of architecture by proliferation of small atypical lymphoid cells in sinusoidal pattern. Scattered medium sized cells were seen along with large cells in characteristic perivascular arrangement. (Figure 3) Well

defined granulomas were also noted in the parenchyma (Inset in Figure 3). "Hallmark cells" were seen occasionally.

At immunohistochemistry tumor cells showed positivity for leukocyte common antigen, epithelial membrane antigen and CD3. In addition, weak CD30 positivity in small cells and strong CD30 positivity in large cells was noted. ALK protein was positive in all the cells. Hence a final diagnosis of small cell variant of ALK+ ALCL with granulomatous reaction was made.

Patient is doing well 14 months post chemotherapy cycles.

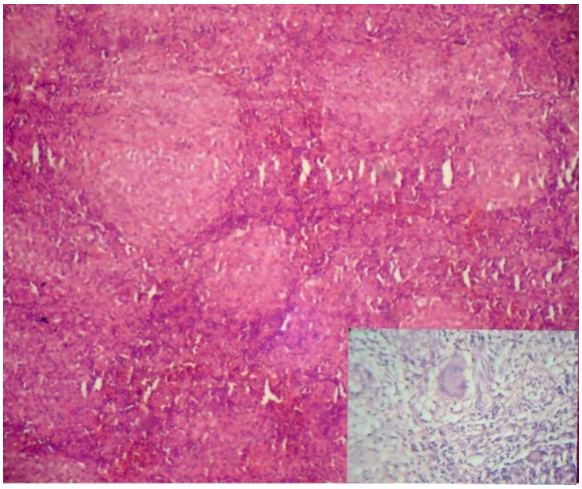

Figure 3: Histopathology section showing perivascular arrangement of tumor Cells (Inset show granulomatous reaction). (H & E × 100)

DISCUSSION

Pathologists frequently encounter granulomatous reaction in routine surgical pathology in variety of neoplastic process. These include Hodgkin's lymphoma, carcinoma, NHL, seminoma and rarely sarcoma. Granulomatous reaction is seen relatively more commonly i.e., 2 to 29%, in Hodgkin's lymphoma as compared to NHL in which it accounts for 2 to 7% cases. [3, 4] ALCL is a novel group of lymphoma constituting 2-8% of NHL in adults and 20 to 30% of large cell lymphomas in children, CD 30 positivity and ALK protein expression being the defining marker. [5]

Morphologically ALCL presents a wide spectrum ranging from common type, lymphohistiocytic, small cell, giant cell rich, Hodgkin like and sarcomatoid variant. Identifying these subgroups is critical as they are easily mistaken for inflammatory lesion or a lymphoma other than ALCL.

Small cell ALCL is enigmatic, since presence of small cells and scarcity of typical "hallmark" cells poses diagnostic difficulties especially at cytology. More over presence of granulomatous reaction may obscure the underrepresented neoplastic cells tempting to think about an infectious or inflammatory disease, leading to delay in arriving at an accurate diagnosis. Association of granulomatous reactions with ALCL is not very common. Careful search of literature revealed only one case report of concomitant occurrence of granulomatous reactions in ALCL. [1]

At cytology small cell variant of ALCL show heterogeneous population of small lymphoid cells admixed with few intermediate and large cells along with occasional neutrophils, eosinophils and

plasmacytoid cells . Small lymphocytes have irregular nuclear membrane, coarse chromatin and prominent round or tubular nucleoli. Careful search should be made for "hallmark" or "embryoid cells". [6] These are large cells with horse shoe shaped nucleus, abundant amphophilic cytoplasm and a perinuclear hoff in May Grunwald Giemsa stain. Unlike the common type of ALCL in which "hallmark cells" is numerous, they are rarely noticed in small cell variant. [7] Nevertheless, these cells are present universally in all the variants of ALCL; hence they were named as "hallmark" cells. Based on cytology alone, diagnosis of this uncommon variant, especially when accompanied by granulomatous reaction, is challenging and should be suspected in an appropriate clinical setting. Ng Wk et al in their review of 10 FNAC samples from 8 patients of ALCL, have described in detail the cytological findings and emphasised the significance of application of immunocytochemical staining on cell block sections for accurate diagnosis. [8]

At histopathology, like the common type ALCL, small cells are arranged in cohesive sheets in sinusoidal pattern. Large cells arranged in perivascular pattern are consistently present and is considered characteristic of small cell variant. These large cells show CD 30 positivity and demonstrate ALK protein expression. [9] Although histology and immunohistochemistry of ALCL have been well documented, FNAC has been underreported especially in the small cell variant cases. [6]

In our case careful attention to nuclear morphology of small lymphocytes and diligent search for "hallmark cells" would have avoided the delay in diagnosis.

Though exact mechanism of occurrence of a granulomatous response in a lymphoma is not fully understood, it is thought to be related to cytokine production by tumor cells or surrounding reactive cells. [10] Presence of granulomatous reaction in NHL has no prognostic significance, however it inevitably leads to delay in diagnosis and treatment. [11]

Small cell variant of ALCL behaves aggressively as compared to other subgroups of ALK+ ALCL, many showing leukemic involvement at presentation. They may progress to common type ALCL, the fact that reinforces the need for early diagnosis and treatment. [12]

CONCLUSION

Presence of epithelioid granulomas at cytology should prompt a pathologist to relook and consider a lymphoma in the differential diagnosis in appropriate clinical settings to avoid delay in accurate diagnosis and initiating treatment. Small cell ALCL can be easily mistaken for inflammatory lesion especially so when accompanied by granulomatous reaction. A multi-disciplinary approach with awareness of this uncommon variant, high degree of suspicion in a young patient with peripheral lymphadenopathy, careful examination of the cell morphology and liberal use of CD 30 and ALK protein in a T cell lymphoma is advocated.

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