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Case Report

Sinister Cells When Least Expected: Follicular Centre Cell Lymphoma Spill Over, An Incidental Finding

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Abstract

Background: Follicular Lymphoma (FL) constitutes 5% of all hematological neoplasms, being second most common neoplasm amongst all non-Hodgkin lymphomas. Most commonly seen in middle age with M:F ratio 1:1.7.

Case Report: 42 year male, cervical swelling, initially diagnosed as Reactive Lymphoid Hyperplasia, was later diagnosed as FL grade II on excisional biopsy with CD 10, CD20, Bcl 2 and Bcl 6 positive and CD 3, CD 5, CD 23 negative in tumor cells. Peripheral blood showed 21% atypical lymphoid cells. Flow cytometry revealed cells positive for CD 19. Of these, CD 10 and CD 20 were 82.45% dim and 99.95% dim to moderate positivity respectively. CD 5, CD 23, CD 38, CD 200 were negative.

Discussion: Follicular lymphoma is an indolent B cell lymphoproliferative disorder. Tumor develops in precursor B cells in germinal centre of lymph node, hence treatment with Rituximab shows good response. However, identifying a spillover is essential for adequate treatment.

Keywords: Follicular Lymphoma; Non Hodgkin Lymphoma; Lymphoproliferative Disorder; Spillover

Introduction

Follicular centre cell lymphoma (FCCL) is a neoplasm of the lymphoid tissue showing germinal centre (GC) B-cell differentiation constituting ~20-25% of all new Non-Hodgkin lymphoma (NHL), diagnosed in western countries [1]. It is an indolent lymphoma having highly favourable outcome, although some of the patients are at risk of disease progression and adverse outcomes [1]. About 80% of all FCCLs show systemic nodal involvement with peripheral cervical and inguinal lymph nodes being most commonly involved. Most commonly seen in middle aged individuals and elderly, around 85% of the patients have t (14;18) resulting in the overexpression of the BCL2 oncogene [2]. Average male to female ratio is 1:1.7 [3]. Treating FCCL with Rituximab has resulted in an overall survival of more than 10 years in approximately 80% of the patients. However, the identification of patients at high risk who might need alternative therapies to the current standard treatment is a growing need that will help direct clinical trial research [1]. Hence identifying a case of spill over of lymphoma in blood and/or bone marrow involvement is essential for adequate treatment to the patient.

However, there is very limited literature regarding spillover in blood in FCCL.

Case Report

A 42 year old male presented with a cervical swelling on the right side for the past 6 months and was sent for haematological workup. Peripheral blood showed leucocytosis with Total Leukocyte Count (TLC) of 17,000/mm3 and relative lymphocytosis with

normocytic normochromic anemia (Hemoglobin: 7.4gm/dl). The platelet count was normal. White Blood Cell (WBC) scattergram plot showed two distinct clusters in the lymphocytic window suggesting two population of lymphocytes (Figure 1a), with peripheral smear showing 21% atypical lymphoid cells (Figure 1b). Flow cytometry (FCM) was performed on the peripheral blood, which showed 45% cells in lymphoid window, out of which 24.2% cells were CD 19 positive. Of these cells, CD10 and CD20 expression was 82.45% dim and 99.95% dim to moderate respectively. 54.47% of these cells showed Kappa restriction with dim to moderate positivity. Other positive markers included FMC7 (51.6% dim) and CD81 (45.46% dim). Lambda, CD38, CD5, CD23, and CD200 were all negative (Figure 2). Communication with the clinician revealed that the patient also had associated mild fever, on and off, cough and severe abdominal pain. Cervical examination showed level II, III, IV and V nodes to be enlarged, firm and matted (Figure 3a). CECT revealed multiple homogeneously enhancing enlarged discrete and conglomerated lymph nodes (LN) in the retroperitoneum, alongwith superficial inguinal and epiphrenic regions, largest measuring 3.3 x 2.9 cm in the right external iliac area, as well as in the cervical region (Figure 3b). Fine needle aspiration cytology (FNAC) revealed features of lymphoproliferative neoplasm (Figure 3c). This was followed by excisional LN biopsy which showed maintained nodal architecture, with >75% of follicular area and attenuated mantle zone. The follicles composed of centrocytes and centroblasts, with 6-7 centroblast/high power field (hpf). The subcapsular sinuses were involved along with perinodal extension of neoplastic cells. Morphology was suggestive of Grade II FCCL (as per Mann and Berrard histological scoring system system) (Figure 4a). This was further confirmed by immunohistochemistry (IHC) which showed CD20, CD10 and BCL2 expression in the follicles with CD3 and Bcl6 being expressed in interfollicular areas. CD5 and CD23 were negative in the neoplastic follicles (figure 4b, c, d, e). Thus, the final report was given as FCCL with follicular centre cells spill over in the peripheral blood.

Discussion

A cell NHL make about 80% of the NHL [4]. The most common subtypes include FCCL, diffuse large B-cell lymphoma (DLBL), marginal zone lymphoma and mantle cell lymphoma [5]. DLBL NHL is the most common subtype (60%) followed by FCCL (12-20%) [6].

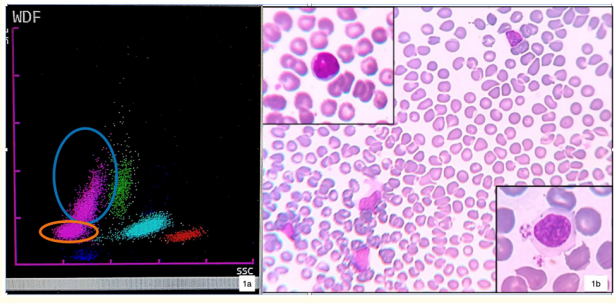

Figure 1: a: Scattergram showing dual population of lymphocytes in lymphocyte window. 1b: Peripheral smear showing atypical lymphoid cell 1.5-2 times the size of small lymphocytes with abundant basophilic cytoplasm and opened up chromatin (Giemsa stain, 400x). Inset: upper left corner-atypical lymphoid cell (Giemsa stain, 400x); right lower corner- atypical lymphoid cell (Giemsa stain, 1000x)

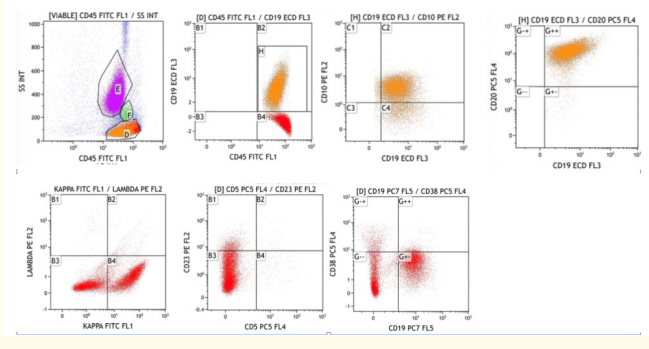

Figure 2: CD 45 vs SS: 45% cells gated in lymphocyte window. Out of these, 54.86% are positive for CD 19 and 79.23% show coexpression of CD 10 and CD 19.
99% of these cells coexpress CD 19 and CD 20. 54.5% of the atypical cells show kappa light chain restriction. The cells are negative for CD 38 , CD 5 and CD 23.

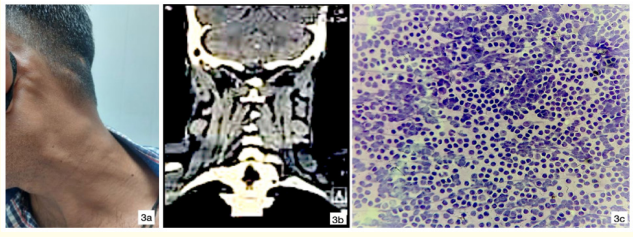

Figure 3a: Cervical examination showed multiple enlarged lymph nodes.

Figure 3b: CECT shows multiple cervical lymph node showing multiple homogeneously enhanced lymph nodes.

Figure 3c: FNAC from cervical nodes shows monomorphic population of centrocytes and centroblasts with presence of small and large lymphocytes (H and E stain 600x).

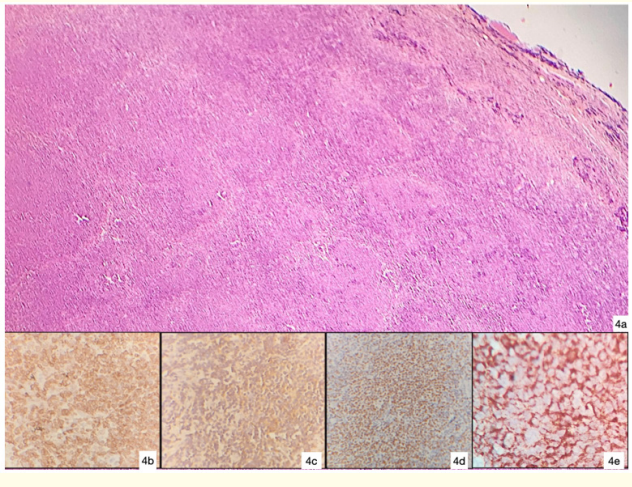

Figure 4: a: Biopsy of the same case shows neoplastic follicles of equal size. 4b,c: Immunostain for Bcl 2 and CD10 showing membranous positivity. 4d: Immunostain with Bcl 6 show nuclear positivity. 4e: immunostain with CD 20 show (H and E stain, 600x).

FCCL is an indolent B cell lymphoproliferative disorder, where the patient presents with diffuse lymphadenopathy, bone marrow involvement, and splenomegaly. Less commonly, extranodal involvement is seen. Presence of constitutional symptoms like fever, night sweats, and weight loss usually herald transformation to DLBL [7].

Histopathological examination showed retained follicular architecture with the follicles showing neoplastic cells, which are centrocytes (small to medium sized cells) and centroblasts (large cells) with the latter indicating clinical aggressiveness of the disease [6]. The WHO classification grades the FCCL as Grade I which has 0 to 5 centroblasts/hpf and Grade II showing 6 to 15 centroblasts/hpf, both with a follicular or diffuse pattern. Grade III, further subdivided into IIIa, showing centrocytes and IIIb showing sheets of centroblasts with percentage of follicular and diffuse component [7]. Grade IIIb is clinically treated as DLBL. FCCL involves the bone marrow with characteristic paratrabecular lymphoid aggregates. IHC show monoclonal immunoglobulin light chain, CD19, CD20, CD10, BCL-6, and overexpress BCL-2, due to t (14;18) and are negative for CD5 and CD23 [8].

Involvement of blood by other NHL, mainly by mantle cell lymphoma, nodal zone lymphoma, DLBL, small lymphocytic lymphoma/chronic lymphocytic lymphoma, Burkitt's lymphoma, is quite common, and multiple cases have been reported till date and has been studied extensively.

However, FCCL spill over in blood has very limited literature in the world of hematology. In the study by Sarkozy C., *et al*. FCCL showing peripheral blood spill over, has been associated with a shorter progression free survival and overall survival [9]. Presence of FCCL leukaemia phase is considered to be an independent prognostic factor for time to progression [9]. In the study by Alnawakil C., *et al*. similar leukaemic involvement has been considered as an atypical presentation with an indolent course of disease, but no association with prognosis has been suggested [10].

E.Beltran B., *et al*. conducted a study in the USA describing 7 cases of FL with leukaemia spillover and compared them with 24 cases reported in literature. They found cases with leukemia spillover tend to have worse prognosis. They also suggested that the difference in prognosis could be attributed to difference in geographical regions [11].

Current case showed leukemia spillover with peripheral blood involvement showing 21% atypical lymphoid cells which were fur-

ther confirmed by FCM, showing expression of the FCCL markers CD19, CD20, CD10 and FMC7 with negative CD5, CD 38, and CD23. However patient has been kept under strict follow up and is doing well till the publication of the paper, similar to the study by Al-nawakil C., *et al*. [10].

Leukaemia spill over of lymphoma should be strictly followed up and treated accordingly for which high index of suspicion and proactiveness should be adopted for better management of such cases.

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