

## CASE REPORT

**Leg Edema Unveiled: The Uncommon Culprit of Follicular Lymphoma**Syed Muhammad Ibn e Ali Jaffari<sup>1</sup>, Samaha Nisar<sup>2</sup>, Narjis Malik<sup>3</sup>, Syed Muhammad Aun Ali Jaffari<sup>4</sup>, Omar Nisar<sup>5</sup>Shalamar Medical and Dental College, Lahore, Pakistan<sup>1,2,3,5</sup>  
Lahore Medical and Dental College, Lahore, Pakistan<sup>4</sup>**ABSTRACT**

Follicular Lymphoma is a type of non-Hodgkin's Lymphoma. It is defined as a lymphoma of germinal center B cells and a complex disease involving genetic and epigenetic mutations of Follicular B cell. We report a 50 years old patient here who presented with gross and progressing edema of the right lower limb that started in the foot and progressed proximally up to the thigh. Fine Needle Aspiration Cytology was false negative but after much delay an ultrasound guided core biopsy confirmed the diagnosis of follicular lymphoma. The aim of this case report is to highlight the significance of clinical co-relation between leg edema and follicular lymphoma and the diagnostic approach for Follicular Lymphoma's early detection and treatment.

**Keywords:** Follicular lymphoma; Malignancy; Non-Hodgkin's lymphoma; B-cell neoplasm; leg edema; swelling.

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**INTRODUCTION**

Follicular Lymphoma is a type of Non-Hodgkin's Lymphoma. It is defined as a lymphoma of germinal center B cells.<sup>1</sup> A lot of diagnostic challenges are being faced as this disease is indolent and presents atypical features. The gold standard is an excisional biopsy and FNAC can yield false positive misleading the diagnosis.<sup>2</sup> Here, we report a case of 50 years old female who presented with edema of the right lower limb that turned out to be Follicular Lymphoma.

**CASE REPORT**

A 50-year-old female presented in outpatient department of Shalamar Hospital with 6 months history of progressive swelling of the right lower limb. She had diffuse pain in right lower limb, it started as swelling of the right foot which gradually progressed, proximally involving calf, and thigh and groin region. There was difficulty while walking.

It was grossly swollen as compared to the left limb. There was no history of night sweats, fever, weight loss, intermittent claudication, headache or skin rash. She was married 23 years

back and had 2 kids of aged 21 and 19. Medical history revealed menstrual irregularities and decreased platelet count due to which patient was diagnosed with Immune Thrombocytopenia purpura (ITP) 10 years ago. She was treated with low dose steroids and Danazol which led to improvement of symptoms.

Physical examination of the patient revealed middle aged lady, fair looking, with mild pain and grossly edematous right lower limb. The overlying skin was dull and there was non-pitting edema with no pain on palpation. Lymph nodes were not palpable in the axilla, neck, left groin. The right flank and loin appeared full and a mass was suspected. There were no visible veins but the arteries of right lower limb such dorsal pedis, popliteal and femoral were not palpable due to the gross edema of the right leg. Abdomen was soft with no tenderness on palpation, normal bowel sounds, no rebound tenderness or visceromegaly. Chest examination was unremarkable. The Blood analysis only revealed thrombocytopenia i.e., Platelets count of  $115 \times 10^9/l$ . All other investigations including serum LDH, Serum CRP and Serum Beta-2 Micro

globulin were within the reference range. Quantiferon TB gold plus was negative as well. HBV and HCV status were negative.

On ultrasonography, a mass with thick hyper echoic shadows were seen along with the right abdominal wall in right iliac fossa. No pleural ascites and visceromegaly was seen. Doppler Ultrasound was ordered and it ruled out Deep Venous Thrombosis. An ultra-sounded guided biopsy of abdominal and right iliac fossa lymph nodes was performed and specimens were sent to the laboratory. The Histological examination of the sections revealed fibrin clot with inflammatory cells (Lymphocytes) showing crushed artifact. No malignancy was seen. The FNAC of right iliac fossa lymph node (Figure 1) was also done and cytological examination of the smears show hemorrhagic background which are seen polymorphous population of lymphoid series cells comprising mature lymphocytes. No Atypical cells were seen.

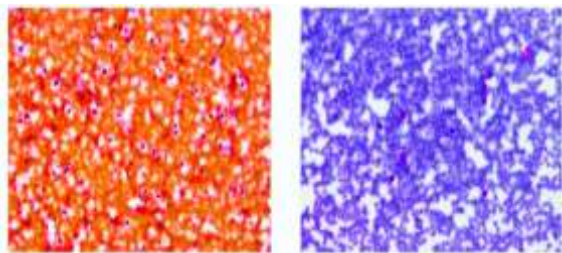


Figure 1: FNAC Right Iliac Fossa Lymph Node Biopsy

FNAC shows polymorphous population of lymphoid series cells comprising of mature lymphocytes on hemorrhagic background. No atypical seen.

Later, an ultra-sound guided core biopsy was performed and Histopathological report showed tissue cores with lymphoid neoplasm composed of closely packed follicles with absence of tangible body macrophages and polarization. They showed predominantly small cleaved cells with more than 15 large cells/HPF.

The immune/ Histochemical stains showed CD20 positive, BCL2 positive, Ki67 10% proliferation index and BCL6 positive as well. The diagnosis of B-cell Non-Hodgkin

Lymphoma consistent with Low grade follicular Lymphoma was made.

In November 2020, Whole Body Positron Emission Tomography (PET)/CT Fluoro-deoxy Glucose (FDG) Imaging was done and it showed that there is significant volume FDG avid peritoneal and retroperitoneal abdominopelvic adenopathy occupying the paraaortic recesses commencing at the level of renal hilar vessels and extending along the pelvic side walls up to the inguinal regions. There were metabolically active soft tissue nodules in the intermuscular planes of the gluteus maximus and medius muscles of gluteal regions bilaterally. Metabolically active mediastinal adenopathy was noted occupying subcarinal and aorto-vertebral triangles.

The Final impression was metabolically active nodal disease above and below the diaphragm with FDG avid soft tissue nodules in the intermuscular planes of the bilateral gluteal regions. No evidence of visceral or osseous involvement was observed.

The patient was referred to Midcity Hospital where she was treated with Bendamustine combined with Rituximab every 28 days for 6 months. The leg swelling drastically improved with every chemotherapy and immunotherapy session. The thrombocytopenia also improved with every session. After six months, another follow-up PET scan was performed in May 2021 to see the residual disease and it showed Comparison to PET-CT dated Nov, 2020.

Previously noted significantly FDG avid retroperitoneal adenopathy involving the paraaortic as well as the pelvic side wall recesses has shown significant interval response.

The Final Impression was partial metabolic and morphologic response with residual paraaortic and right pelvic side wall lymph nodes with mild metabolic activity seen.

After 6 months of Chemotherapy and immunotherapy, the patient was on maintenance therapy with Rituximab for two years when she

was infected with Coronavirus (Covid-19) SARS Cov2 and died on 1st October 2021.

## DISCUSSION

This study emphasizes on a case of Follicular Lymphoma (FL), the second most common type of Non-Hodgkin Lymphoma (NHL),<sup>3</sup> Comprising of 20-25% of all newly diagnosed NHL and 5% of all hematologic malignancies around the world<sup>4</sup> and an alarming rise has been seen in Pakistan as well.<sup>5</sup>

The main challenge faced during this case was the diagnosis of follicular lymphoma. The disease is mostly asymptomatic. Patients may present with B symptoms such as fever, fatigue, weight loss, night sweats, or recurrent infections (seen in 10% of patients). This patient presented with leg swelling which is a rare symptom of the disease, especially when generalized lymphadenopathy was not present. 95% of unilateral non-pitting edema of lower limb is due to lymphatic obstruction secondary to infection, surgery or malignancy.<sup>7</sup>

10-20% cases of follicular lymphoma remain localized, while mostly present with widespread involvement (80%) and advanced stage disease.<sup>8</sup> Another prominent finding in this case which is rare in patients with FL is thrombocytopenia. In a past study, only 5 of 33 patients with follicular lymphoma turned out to have thrombocytopenia. Other extra nodal manifestations could be anemia and leukopenia, which are not seen in this patient. Involvement of mucosal sites can also be seen in a few cases which can be asymptomatic or symptomatic.<sup>4</sup>

The first imaging done here was ultrasonography which showed non-specific disease. Lymph node biopsy such as needle biopsy and excisional biopsy are frequently used diagnostic techniques. Needle biopsy includes both fine needle aspiration cytology and core biopsy.<sup>4</sup> In this case, the fine needle aspiration cytology (FNAC) was false negative. In past literature, fine needle aspirations have not been proved to be reliable for ruling out diagnosis,<sup>9</sup>

thus a core biopsy is usually performed in such cases.

FL is believed to arise from B-cell proliferation of germinal centers including centrocyte and centroblasts, and so stained positive for germinal center antigens i.e., CD 10 and CD 20 as present in this patient.<sup>8</sup> The common use of immunophenotyping has led to ease in diagnosing and classifying the tumors of immune system, one of which is being Follicular Lymphoma.<sup>8</sup> This technique has led to a decrease in observational error and increase in reproducibility of results. In a study where diagnosis was based only on histology was compared to that made with histology, immunophenotype and clinical data, accuracy in diagnosis of FL was raised up to 94%.<sup>8</sup>

A Positron Emission Tomography (PET)-CT was performed to stage the disease. It is recommended in routine screening as it improves the accuracy of staging of follicular lymphoma in nodal as well as extra-nodal disease.<sup>9</sup> To further elaborate this point, a study worth mentioning used fluorodeoxyglucose-PET scan to stage FL. In about 30% of the patients, stage I and II were upgraded to stage III and IV by PET, and 14% patients required modification in their radiation therapy.<sup>10</sup>

Lactate Dehydrogenase (LDH) and  $\beta$ 2-microglobulins (B2M) levels are known as markers of disease progression and are known to be associated with overall-survival rate. B2M levels were also included in Follicular Lymphoma International Prognostic Index (FLIPI) which is used to evaluate prognostic score of patients with FL. Overall rise in level of B2M is seen in only 15% of the patients<sup>4</sup> and level of LDH was seen to rise in 20% of patients.<sup>6</sup>

These markers were normal in our case and showed the tumor to be have a good prognosis.

Follicular lymphoma International Prognostic Index (FLIPI 1 & 2).<sup>12</sup>

Characteristics	Poor Factors	
	FLIPI-1	FLIPI-2
Lymph Node	>4 areas of lymph node	Maximal diameter of lymph node >6 cm
Age, years	>60	>60
Serum Marker	Increase LDH	Increase $\beta$ 2-microglobulin
Staging	Late Stage (Ann Arbor III-IV)	Bone marrow violated
Hemoglobin	<12 g/dl	<12 g/dl
Low risk, 0-1; Intermediate Risk, 2; High Risk, 3-5		

Another marker to grade follicular lymphoma is “Ki-67 proliferation index”. This index evaluates the rate of proliferation of cells and thus lower index correlates to lower grade. When checked in our patient, it turned out to be 10%. Low grade Follicular Lymphomas usually have rates lower than 20%,<sup>4</sup> thus our case can be classified as low-grade follicular lymphoma.

Treatment for patients with follicular lymphoma can be done through various approaches, however, in a number of cases such as this one, it is expected that patient may not be able to tolerate the toxicity associated with multiple drugs. As shown in a phase III trial on Non-Hodgkin’s Lymphoma showed Bendamustine plus Rituximab (BR) to have a superiority in effectiveness and tolerability as compared to others,<sup>11</sup> our patient was also treated with the same BR regimen.

## CONCLUSION

In conclusion, follicular lymphoma mostly presents as asymptomatic disease or showing nodal or extra-nodal involvement. Disease presentation can be as vague as waxing and waning leg edema and thrombocytopenia as given in this case. The real challenge is to diagnose the disease as early diagnosis and treatment has good overall survival and better PFS. Tissue biopsy and excisional biopsy of involved lymph nodes can be used to as diagnostic tests with FNAC having less sensitivity as compared to core biopsy.

Various markers of disease progression and survival can be used such as LDH and  $\beta$ 2-microglobulins, overall survival score can be calculated through FLIPI-2 criterion. All these investigations are to be performed in a suspicion of Follicular Lymphoma for diagnosis, staging and management.

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