

## CASE REPORT

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# Composite lymphoma of the axillary lymph node comprising peripheral T-cell lymphoma-not otherwise specified and follicular B-cell lymphoma: A case report

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## ABSTRACT

**Introduction:** Composite lymphoma is defined as coexistence of two or more morphologically and phenotypically distinct lymphomas in the same anatomical site. Composite lymphoma may include combinations of Hodgkin lymphoma (HL) and B- or T-cell non-Hodgkin lymphoma (NHL); B-cell NHL and T-cell NHL; or two distinct B-cell or T-cell NHLs. The exact pathogenesis of composite lymphoma is unknown. Most cases demonstrate poor outcomes with a median survival of 12 months. The treatment is usually directed toward the higher-grade component.

**Case Report:** Here, we report an extraordinarily rare case of a composite lymphoma composed of peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) and follicular B-cell lymphoma (FBCL) coexisting in a single axillary lymph node in a 66-year-old female.

**Conclusion:** The medical literature lacks significant information regarding this type of composite lymphoma, thus creating a challenge for management. Currently, only one other case of this type of composite lymphoma has been reported in the English medical literature, with this case reporting the first female patient.

**Keywords:** Composite lymphoma, Follicular lymphoma, Peripheral T-cell lymphoma

### How to cite this article

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## INTRODUCTION

Composite lymphoma (CL) is characterized as a lymphoma with two distinctly different types of lymphoma located at a single anatomic site or mass [1]. The most common subtype is B-cell lymphoma with HL or NHL [2, 3]. B-cell lymphomas have been documented to coexist with other T-cell lymphomas, however, at a much rare frequency. The majority of coexisting B- and T-cell CLs are either diffuse large B-cell lymphoma with PTCL or diffuse large B-cell lymphoma with angioimmunoblastic T-cell lymphoma [4].

Diagnosis of CL requires a biopsy with subsequent histological, immunohistochemical, and molecular investigation. This group of lymphomas demonstrates different morphological types in one lymph node. If the different morphological types arise in different anatomical locations, this may be termed a simultaneous lymphoma. If the CL occurs in the same organ, it may demonstrate sharp or diffuse borders separating the two

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different lymphomas or partial mixtures of cell types derived from the different lymphomas that are present. Immunohistochemical markers help to define the bystander cells and facilitate the determination of which lymphomas exist in the sample [4].

Follicular lymphomas, or FBCLs, are a prototypical type of B-cell lymphomas. This cancer originates from centrocytes and centroblasts that lie in the germinal centers of lymph nodes and proliferate to form follicle-like structures in these tissues [5]. Immunohistochemically, these cells classically express CD20, BCL2, BCL6, and CD10 [4]. In asymptomatic patients, these lymphomas may be observed over time to monitor progression. Symptomatic FBCL, however, can be treated using the CVP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen with added rituximab therapy [5].

Peripheral T-cell lymphomas (PTCLs) are a more aggressive and malignant group of lymphomas that are derived from mature T-cells. The most common subtypes are PTCL-NOS (which is the most common), angioimmunoblastic T-cell lymphoma, and anaplastic lymphoma kinase (ALK)-positive or ALK-negative anaplastic large cell lymphoma. A combination of CHOP, with or without rituximab (R-CHOP), has been the historical backbone of PTCL treatment; however, this regimen is associated with low complete remission rates and poor overall survival rates [6]. Using autologous stem cell transplant (ASCT) in consolidation with this chemotherapeutic approach, however, has been shown to improve these overall survival rates from these lymphomatous neoplasms [7].

We report an extraordinarily rare case of a 66-year-old female with a CL composed of PTCL-NOS and FBCL in a single axillary lymph node. The medical literature lacks significant information regarding this type of CL, thus creating a challenge for management. Currently, only one other case of CL of this type has been reported in the English medical literature, with this case reporting the first female patient.

## CASE REPORT

A 66-year-old female smoker initially presented with generalized lymphadenopathy, B symptoms (fever, night sweats, and weight loss), hypercalcemia, and exudative right-sided pleural effusion. The patient had a past medical history of type two diabetes mellitus, hypertension, and hyperlipidemia. Her social history was significant for one pack per day smoking history. She had an Eastern Cooperative Oncology Group (ECOG) status of one at the initial encounter. Complete blood count (CBC) was positive for moderate normocytic normochromic anemia and mild thrombocytopenia. Subsequent positron emission tomography (PET) composite tomography (CT) scan revealed generalized metabolically

active lymphadenopathy (Figure 1A). The patient underwent surgical biopsy of the left axillary lymph node. Histopathology showed effacement of the architecture due to an atypical follicular proliferation composed of follicles varying in size (Figure 2). The follicular component was consistent with a diagnosis of follicular lymphoma (grade 3A) with centrocytes and centroblasts (Figure 3). The follicles demonstrated positivity for CD20, CD23, BCL2, BCL6 (Figure 4A–D), CD79, OCT2, and MUM1. There was a polymorphic population of cells in the background that showed positivity for CD3, CD5, CD2, CD7 (with partial loss), CD30 and CD43 (Figure 5A–D). Epstein–Barr virus (EBV) B-cells were also expanded (Figure 6). Based on the morphology and immunohistochemistry (IHC), diagnosis of PTCL-NOS with a high proliferative index was favored in the atypical T-cell population (Figure 5C). Fluorescent in situ hybridization (FISH) assay was performed on the left axillary lymph node specimen, demonstrating positivity for rearrangement involving BCL6 (35% of cells) and negativity for rearrangement of BCL2.

A bone marrow biopsy was obtained to undergo further analysis. There were no chromosomal abnormalities detected on cytogenetic analysis of this sample, and the karyotype was 46,XX. Polymerase chain reaction (PCR) analysis was performed on the bone marrow specimen for B- and T-cell clonality. Clonal B-cell population was detected positive for IgH gene rearrangement and clonal T-cell population positive for T-cell receptor gamma gene rearrangement. T-cell receptor gamma gene rearrangement was also positive in left axillary lymph node specimen. Clonal Ig kappa rearrangement was detected, while FR1, FR2, and FR3 were polyclonal. These molecular findings further supported a diagnosis of composite lymphoma of B- and T-cell lineage.

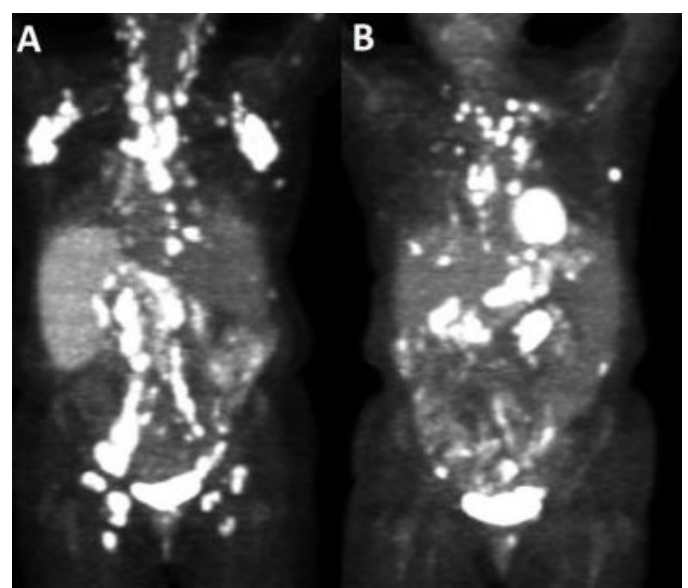


Figure 1: (A) PET-CT scan prior to chemotherapy; (B) PET-CT scan after chemotherapy demonstrating partial response.



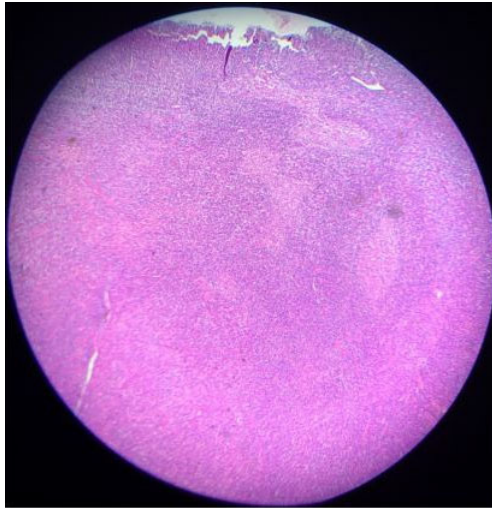


Figure 2: Hematoxylin and eosin stain of the excisional biopsy specimen revealing effacement of the lymph node architecture due to an atypical follicular proliferation with follicles varying in size ( $\times 20$ ).

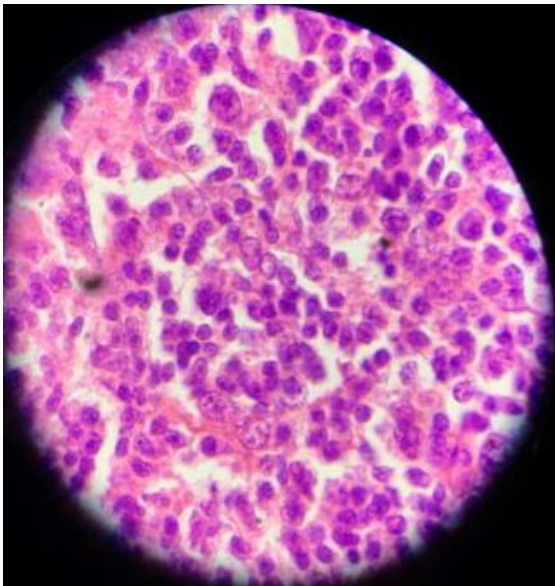


Figure 3: Hematoxylin and eosin stain demonstrating follicular lymphoma (grade 3A) with centrocytes and centroblasts ( $\times 600$ ).

The recurrent hypercalcemia was treated with pamidronate while awaiting the diagnosis. PTCL-NOS is the most aggressive of the two lymphomas, so the patient underwent six cycles of a chemotherapy regimen to specifically target that component. She was treated with brentuximab vedotin 1.8 mg/kg intravenous (IV), cyclophosphamide 750 mg/m<sup>2</sup> IV, doxorubicin 50 mg/m<sup>2</sup> IV on the first day of each cycle. On days 1–5 of each cycle, prednisone 100 mg PO daily was introduced (BV+CHP). Subsequent PET-CT scan post-BV+CHP therapy showed a partial response (Figure 1B). The patient is now awaiting post-treatment lymph node excisional biopsy followed by autologous stem cell transplant evaluation.

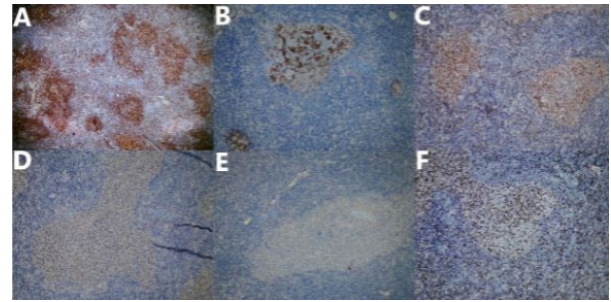


Figure 4: (A) Immunohistochemical staining demonstrating positivity for CD20 of the follicular lymphoma cells ( $\times 40$ ); (B) Immunohistochemical stain demonstrating the dendritic meshwork of the follicles with positivity for CD23 ( $\times 100$ ); (C) Immunohistochemical stain demonstrating positivity for BCL2 in the follicular lymphoma cells (100); (D) Immunohistochemical stain demonstrating positivity for BCL6 of follicular lymphoma cells ( $\times 100$ ); (E) Immunohistochemical stain demonstrating negativity for CD10 in the follicular lymphoma cells ( $\times 100$ ); (F) Ki-67 index is high in the neoplastic follicles ( $\times 100$ ).

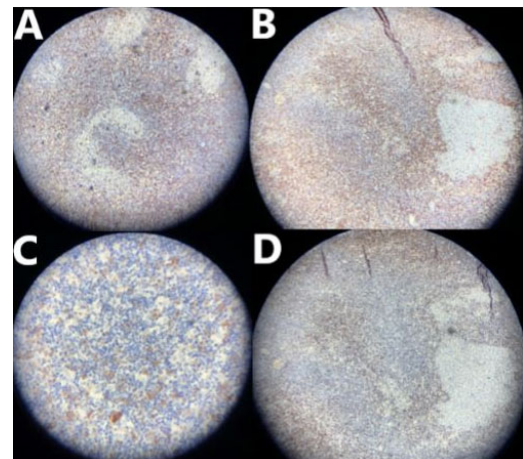


Figure 5: (A) Immunohistochemical stain demonstrating positivity for CD3 in the T-cell lymphoma ( $\times 40$ ); (B) Immunohistochemical stain demonstrating positivity for CD5 in the T-cell lymphoma ( $\times 40$ ); (C) Immunohistochemical stain demonstrating partial loss of CD7 in the T-cell lymphoma ( $\times 40$ ); (D) Immunohistochemical stain demonstrating scattered atypical CD30 positive cells ( $\times 100$ ).

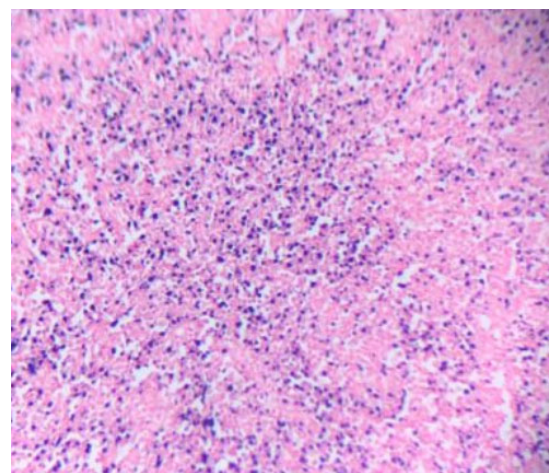


Figure 6: Epstein-Barr encoding region (EBER) in situ hybridization (ISH) revealing expansion of EBV+ cells ( $\times 100$ ).

## DISCUSSION

Composite lymphoma is characterized as a lymphoid neoplasm with two distinctly different types of lymphoma located at a single anatomic site or mass [1]. The incidence varies from 1% to 4.7% of total lymphomas. These neoplasms can arise as having clonal relation or no relation at all between the components. The most common CLs are composed of follicular lymphoma (FL) and mantle cell lymphoma (MCL), FL and chronic lymphocytic leukemia (CLL), FL and nodal marginal zone lymphoma, FL and nodular lymphocyte-predominant HL, and FL and classic Hodgkin lymphoma. T-cell lymphoma associated with low-grade B-cell lymphoma, however, is very rare [8].

This is an exceptionally unique case of CL due to its composition of both PTCL-NOS and FBCL in the same lymph node. The diagnosis was achieved via excisional biopsy of the left axillary lymph node and subsequent histological evaluation and immunohistochemical analysis. Histology demonstrated atypical follicular proliferation with cells staining positive for CD20, CD79, BCL2, BCL6, OCT2, and MUM1. FL Grade 3, thus confirming FBCL. These follicles appeared with an interfollicular background of polymorphic cells, which stained positive for CD3, CD5, CD2, CD7 (with partial loss), CD30, and CD43, confirming PTCL-NOS in concurrence. To our knowledge, a CL with this composition has only been reported in one other case in the medical literature.

Tanaka et al. describe the first case of CL composed of FBCL and PTCL-NOS in a 75-year-old Caucasian male who presented with right neck swelling and fatigue. This patient denied fever, chill, night sweat, and weight loss. Computed tomography (CT) revealed generalized lymphadenopathy involving bilateral cervical, mediastinal, paratracheal, and iliac lymph nodes. Excisional biopsy from the left cervical lymph node revealed T-cell lymphoma with concurrent atypical follicular hyperplasia. Immunohistochemical analyses demonstrated positivity for CD20 and CD3, which revealed B-cells in the lymphoid follicles and T-cells dispersed throughout the interfollicular areas. The interfollicular T-cells were also positive for CD4, PD1, and Bcl6. The follicular B-cells also demonstrated positivity for PAX5, OCT2, CD79a, and CD19. Ki67 stain showed a relatively high proliferative index in the interfollicular areas, whereas follicles appeared in low proliferation. Epstein–Barr virus small RNA was positive in scattered cells in the interfollicular areas. The patient was treated with six cycles of combination chemotherapy that included cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone. Subsequent PET/CT scan revealed persistent lymphadenopathy involving cervical, mediastinal, para-aortic, bilateral iliac, and inguinal lymph nodes, with many of them demonstrating fluorodeoxyglucose (FDG) avid uptake [9].

There have been similar cases reported in the literature. Suefui et al. recorded a single case of CL with

contingents of angioimmunoblastic T-cell lymphoma (AITL) and FBCL (stage 3b) in a 51-year-old male [10]. Angioimmunoblastic T-cell lymphoma is a subtype of PTCL that represents approximately 15–20% of cases. The patients typically present with systemic symptomatology, including generalized lymphadenopathy, B-symptoms, skin rash, pleural effusions, and arthritis. These patients may also demonstrate symptoms related to polyclonal hypergammaglobulinemia, and autoimmune phenomena, such as hemolytic anemia or immune thrombocytopenia. Pathological confirmation on a biopsy is required for the diagnosis. Histology typically shows partial or total effacement of the lymph node architecture with atypical T-cells clustered around the high endothelial venules in a meshwork of follicular dendritic cells. Immunohistochemical staining of neoplastic cells demonstrating positivity for T-cell markers (CD4, CD5, and CD2), as well as T follicular helper (TFH) cell markers (CD10, CXCL13, ICOS, BCL6, and PD1), is critical to confirming the diagnosis. 90% of AITL will also demonstrate positivity for CD30 on IHC [11]. Though this case of AITL is similar to the present case, the PD1 was negative and there is no CD10 and BCL6 positive T-cell population in the present case, making an AITL diagnosis less likely.

The exact pathogenesis of CL is still unknown; however, a few hypotheses exist. One of the more intriguing hypotheses that relate specifically to this reported case hypothesizes that certain viral infections, such as EBV, induce the transformation of two or more separate neoplastic clones, which is particularly significant for mixed T-cell and B-cell neoplasms. In one retrospective study, 44.4% of cases demonstrated positive EBV RNA in neoplastic B-cells, and 100% of the EBV-positive cases were mixed neoplasms [12]. This hypothesis predicts an EBV association with the B-cell component of CL. It is thought that EBV antigens expressed in host B-cells may stimulate T-cell proliferation and eventually induce neoplastic transformation in concurrence with the virus-mediated B-cell lymphomagenesis [12]. The flaw in this theory, however, is that it does not explain the cases of CL that are EBV negative. Other hypothesized mechanisms for the etiology of CL with mixed B- and T-cell origin include a predisposition to developing a second lymphoid neoplasm after having developed or having been treated for a primary lymphoid neoplasm; chronic exposure to antigens that stimulate lymphocyte proliferation; and the exposure to carcinogens that may transform B- and T-cell lineages [12].

Treatment with chemotherapeutic protocols for CL is also challenging due to the paucity of evidence in the literature. The prognosis of composite B- and T-cell lymphomas is most often determined by the more aggressive component [9]. In the present case, treatment was focused on the PTCL-NOS component. The traditional chemotherapeutic regimen for this lymphoid neoplasm includes CHOP with or without rituximab depending on CD20 markers. This regimen, however, is associated with



low complete remission rates and poor overall survival [6]. Recent studies have shown superiority in treating CD30-positive PTCLs with brentuximab vedotin rather than the traditional CHOP therapy [13]. In this case, the patient was treated with a regimen of brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (BV+CHP), which will be followed by post-treatment lymph node excisional biopsy and ASCT.

## CONCLUSION

Here, we report an extraordinarily rare case of CL composed of FBCL and PTCL, confirmed via histopathology and IHC after excisional biopsy of the axillary lymph node. The medical literature lacks significant information regarding this specific type of CL, with only one other case being reported in the English medical literature. With this case, we hope to add to the existing literature to provide data for the identification and treatment for these subtypes of CL. This patient underwent a chemotherapy regimen consisting of BV+CHP in an effort to target the most aggressive component and is currently awaiting evaluation for ASCT.

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## Author Contributions

Sandhya Kolagatla – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Joshua K Jenkins – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Zainab Fatima – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Shweta Chaudhary – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nagabhishek Moka – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

**Guarantor of Submission**

The corresponding author is the guarantor of submission.

**Source of Support**

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**Consent Statement**

Written informed consent was obtained from the patient for publication of this article.

**Conflict of Interest**

Authors declare no conflict of interest.

**Data Availability**

All relevant data are within the paper and its Supporting Information files.

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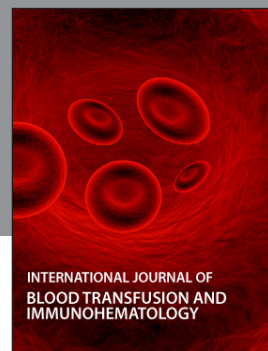
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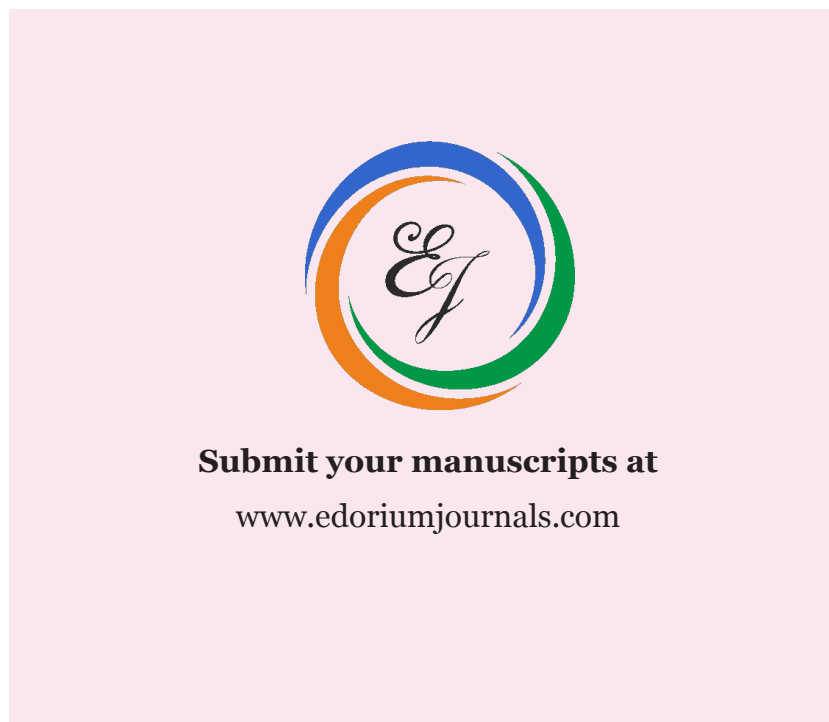
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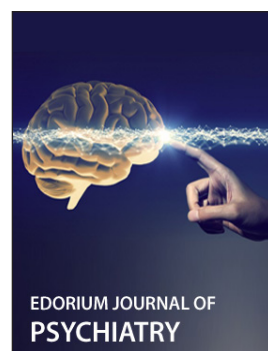
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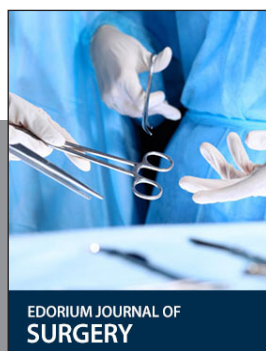
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