



Italian Journal of Medicine

<https://www.italjmed.org/ijm>

eISSN 1877-9352

Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. The Early Access service lets users access peer-reviewed articles well before print/regular issue publication, significantly reducing the time it takes for critical findings to reach the research community.

These articles are searchable and citable by their DOI (Digital Object Identifier).

The **Italian Journal of Medicine** is, therefore, E-publishing PDF files of an early version of manuscripts that have undergone a regular peer review and have been accepted for publication, but have not been through the copyediting, typesetting, pagination, and proofreading processes, which may lead to differences between this version and the final one.

The final version of the manuscript will then appear in a regular issue of the journal.

The E-publishing of this PDF file has been approved by the authors.

Please cite this article as:

Renda M, Scriffignano S, Mancuso S, et al. **What does a fall to the ground hide? An atypical onset of follicular B-cell lymphoma.** *Ital J Med* doi: 10.4081/itjm.2025.1869

Submitted: 25-11-2024

Accepted: 27-11-2024

 © the Author(s), 2025
Licensee PAGEPress, Italy

Note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries should be directed to the corresponding author for the article.

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

What does a fall to the ground hide? An atypical onset of follicular B-cell lymphoma

Maurizio Renda,¹ Silvia Scriffignano,¹ Sabrina Mancuso,¹
Silvana Leanza,² Maurizio Musso,³ Valerio Alaimo⁴

¹Internal Medicine Unit, Fondazione Istituto G. Giglio, Cefalù; ²General Surgery Unit, Fondazione Istituto G. Giglio, Cefalù; ³Oncohematology Unit, Casa di Cura “La Maddalena”, Palermo; ⁴Radiology and Diagnostic Imaging Unit, Fondazione Istituto G. Giglio, Cefalù, Italy

Correspondence: Maurizio Renda, Internal Medicine Unit, Fondazione Istituto G. Giglio, Cefalù, Italy.

E-mail: maurizio.renda@hsrgiglio.it

Key words: follicular B-cell lymphoma, meningeal involvement, atypical clinical onset.

Contributions: MR, SS, SM, MM, clinical diagnostic contribution and bibliographic research; SL, lymph node dissection; VA, radiological diagnostic procedure.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: this is an observational case report that did not involve the use of potentially harmful drugs or therapeutic procedures; in this case, approval from the ethics committee is not required.

Patient consent for publication: patient consent was obtained.

Availability of data and materials: all data underlying the findings are fully available.

Funding: none.

Abstract

Follicular B-cell lymphoma is an indolent B-cell non-Hodgkin lymphoma, typically associated with favorable long-term outcomes and extended survival when diagnosed early. This lymphoma predominantly presents with lymphadenopathy and bone marrow involvement, while central nervous system infiltration remains exceptionally rare, and it has been reported in a few cases. Here, we present a peculiar case of follicular B-cell lymphoma with an unusual neurological onset due to meningeal involvement. Moreover, we studied the histologic expression of the disease in the three different anatomical sites involved: lymph nodes, bone marrow, and dura mater.

Due to the paucity of literature data on this topic, we believe that this clinical case should be worthy of attention to help physicians when dealing with differential diagnosis in patients with neurological symptoms.

Introduction

Follicular B-cell lymphoma, based on the last World Health Organization 5th edition classification and International Consensus Classification, belongs to the group of lymphoid neoplasms that arise from cells that normally develop in B-lymphocytes.¹⁻³ It is a type of B-cell non-Hodgkin lymphoma (NHL) grouped among the indolent ones, due to the relatively better prognosis (median survival as long as 10 years), when diagnosed at an early stage.⁴

The clinical scenario of follicular lymphoma is usually characterized by diffuse lymphadenopathy, bone marrow involvement with or without splenomegaly.⁴ Extra nodal localization, and in particular the central nervous system (CNS) involvement, is rare; based on recent literature data, few clinical cases of follicular B-cell lymphoma with CNS involvement are described.⁵

Therefore, due to the paucity of available literature data on this topic, we described a clinical case of follicular B-cell lymphoma that was peculiar for the CNS involvement and for its onset. Moreover, beyond the characteristic clinical scenario, we compared the histological pattern in lymph nodes, bone marrow, and dura mater, catching the disease expression in different anatomical sites.

Case Report

A 59-year-old woman was admitted to the emergency room of our hospital due to a sudden fall to the ground with loss of consciousness (lasted for about 5 minutes). Her past medical history was characterized by Crohn's disease, arterial hypertension, and favism; no neurological disorder was previously known.

At admission, the patient was alert and oriented, and an urgent encephalon computer tomography (CT) scan was performed: there was a subdural hemorrhage on the right frontal-parietal region with a thickness of 2 cm and an antero-posterior extension of 8 cm with consequent compression of the cerebral parenchyma. Moreover, a minimal haematic layer was present in the contralateral frontal-parietal region (Figure 1).

The first hypothesis was of a subacute subdural hematoma of the right cerebral hemisphere as a post-traumatic one, but the patient reported an episodic and transient clonus of the left foot before the fall. This symptom was a red flag to suspect that the subdural hematoma was the falling cause and not the consequence.

Therefore, an angio cerebral magnetic resonance imaging (MRI) was performed and a hypoplastic P1 posterior cerebral artery was found (on the right), instead on the venous side there was a flux reduction of the superior sagittal sinus. No other vascular abnormalities were found: these findings could not support the clinical scenario.

As a next step, a cerebral MRI was performed: it showed marked and irregular thickening of the dura mater localized at the right frontal-parietal-temporal area and left frontal-parietal area (Figure 2): the high diffuse weighted imaging signal and restricted signal at the apparent diffusion coefficient map were suggestive for a tissue with high cellularity (Figure 2) and after contrast medium it was observed an intense and homogeneous enhancement of the thickened meninges with leptomeningeal involvement.

Based on the meningeal involvement shown at MRI, the hypothesis of a meningeal localization of a lymphoproliferative disease was posed.

The complete blood count, transaminase, and kidney function indices were within the normal range, but erythrocyte sedimentation rate and C-reactive protein were upper the normal range: 41 mm/h (normal range <20) and 36 mg/L (normal range <5), respectively. Creatine phosphokinase and lactate dehydrogenase (LDH) were two times above the upper limit of normal: 298 U/L and 450 U/L.

The general physical examination showed a palpable peripheral lymph node in the right axillar area. Herein, the suspicion of a lympho-proliferative disease was getting stronger, and the 18 fluorodeoxyglucose-positron emission tomography-CT (18FDG-PET-CT) was performed. It detected several positive lymph node areas: right auricular zone and right latero-cervical zone (SUV 8), right axillar area (SUV 10), bilateral iliac area (SUV 13.1), and inguinal-bilateral area (SUV 11.4) (Figure 3).

Therefore, even if the clinical scenario left no room for other diseases reader than lymphoma, to characterized the type of lymphoma, the axillar lympho-nodal biopsy was performed: the lymph node had a subverted architecture with centrocytic and centroblastic cells (less then 5 for high magnification field); the immunohistochemistry showed a lymphoid population characterized by: CD20+, CD3- (small T lymphocytes), CD10+, BCL6+, BCL2(E17)+, CD23-, CICLINA D1-, CD30- and Ki67/MIB1 of 10%. Thus, the lymph nodal histology confirmed a follicular B-cell lymphoma derived from the peripheral B lymphocyte (grade 1-2) with follicular growing.

Even if the bone marrow activity was not increased at the 18FDG-PET-CT, we decided to study the bone marrow involvement by the biopsy, to better define the prognosis: it showed cellularity of 40%, B-lymphoid infiltrate (CD20+) with para-trabecular and pluri-focal distribution, about 10% of cells had centrocytic and centroblastic aspect. This result confirmed the diagnosis of B-cell follicular lymphoma with bone marrow involvement.

The last unexplored site was the meninges, and the most probable hypothesis was a meningeal localization of lymphoma, albeit unusual. Therefore, parietal dura mater biopsy was performed, and the histology findings were compatible with low grade B follicular lymphoma characterized by small-medium B-lymphocytes with diffuse pattern of grow; the immunohistochemistry showed the following cellular phenotype: CD20+, CD23+, CD5-, CD10+, BCL2+>50%, BCL6+ >30%, MUM1-, CD30-, BCL1- and Ki67 of 15%.

During the hospitalization, new symptoms appeared: prurigo sine *materia*, frontal tension, paresthesia (upper and lower extremities), fasciculations of the lower limbs with spontaneous regression, and photophobia. Therefore, the patient had been sent to the Hematological Unit to start the R-CHOP protocol treatment: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Discussion and Conclusions

The recognition of a disease could be very easy when all classical clinical manifestations are present, but it could be very challenging when the onset is “out of the rules”. Therefore, we reported a clinical case of follicular B-cell lymphoma that deserves attention due to its peculiar onset: a fall to the ground. The CNS involvement during a lymphoproliferative disease could configure a primary CNS lymphoma or a primary dural lymphoma.^{6,7}

However, CNS involvement is a rare and unexpected complication of indolent NHL, like follicular B-cell lymphoma, but in case of a previous lymphoma diagnosis, it is appropriate to consider the onset of any neurological disorder as a possible expression of the disease due to CNS involvement.⁸ In particular, the CNS involvement of follicular B-cell lymphoma is rare, and only nine cases have been reported to date, in which the time to CNS relapse varied from a few months to 10 years.⁵

Therefore, we think that our clinical case is worthy of attention due to its rarity: a Follicular B-cell lymphoma that began with neurological symptoms, due to the dura mater involvement. Moreover, the histology of all three involved sites (lymph node, bone marrow, dura mater) confirmed the diagnosis of follicular B-cell lymphoma without any transformation, showing some different aspects of the disease in different anatomical sites.

Even if we did not describe the prognosis in this case, it is known that CNS involvement during low-grade NHL is considered a negative prognostic factor that could follow the diagnosis. For this reason, a risk model was identified with all those factors that could be considered as predictors of the CNS involvement: elevated serum LDH, serum albumin <35 g/L, <60 years of age, retroperitoneal lymph node involvement, and involvement of more than one extra-nodal site.⁹ Therefore, even if it is present a model exists to predict the CNS involvement (after diagnosis), there are no data on the CNS involvement as a starter manifestation during follicular B-cell lymphoma.

In conclusion, we describe a curious clinical case characterized by neurological onset symptoms, which hid a meningeal localization of follicular B-cell lymphoma. We believe that this clinical case could contribute to enrich the scarce literature data on the CNS involvement due B B-cell follicular lymphoma.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia* 2022;36:1720-48.
2. Campo E, Jaffe ES, Cook JR, et al. the international consensus classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. *Blood* 2022;140:1229-53.
3. Jacobsen E. Follicular lymphoma: 2023 update on diagnosis and management. *Am J Hematol* 2022;97:1638-51.
4. Carbone A, Roulland S, Gloghini A, et al. Follicular lymphoma. *Nat Rev Dis Primers* 2019;5:83.
5. Tsuboi Y, Shimizu M, Kuroda A, et al. Follicular lymphoma with secondary central nervous system relapse: a case report and literature review. *Oxf Med Case Reports* 2023;2023:omad118.
6. Schaff LR, Grommes C. Primary central nervous system lymphoma. *Blood* 2022;140:971-9.
7. Karschnia P, Batchelor TT, Jordan JT, et al. Primary dural lymphomas: clinical presentation, management, and outcome. *Cancer* 2020;126:2811-20.
8. Spectre G, Gural A, Amir G, et al. Central nervous system involvement in indolent lymphomas. *Ann Oncol* 2005;16:450-4.
9. Hollender A, Kvaloy S, Nome O, et al. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. *Ann Oncol* 2002;13:1099-107.

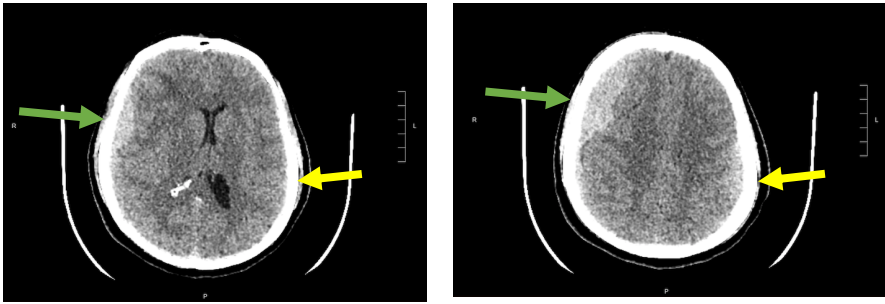


Figure 1. Encephalon computed tomography scan showing subdural hemorrhage in the right frontal-parietal region (green arrow), and a minimal hematic layer was present in the contralateral frontal-parietal region (yellow arrow).

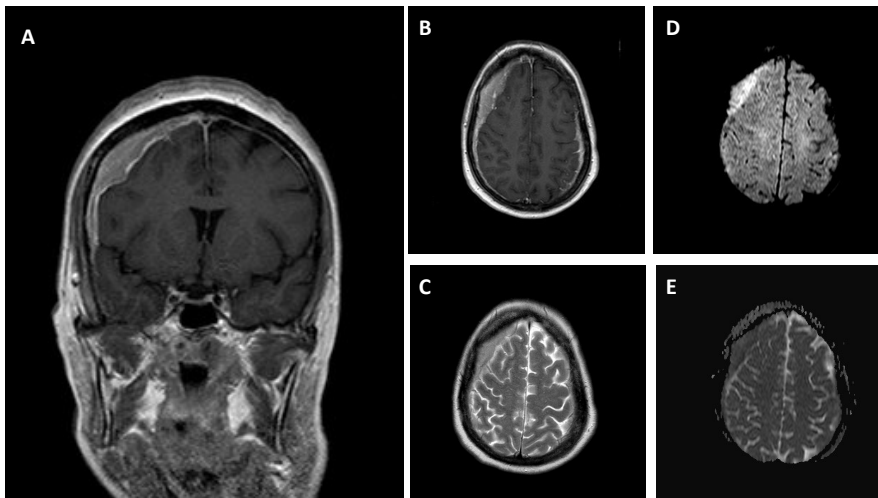


Figure 2. Magnetic resonance imaging showing marked and irregular thickening of the dura mater both at the right frontal-parietal-temporal area (A) and left frontal-parietal area (B). T1 sequences with contrast: intense and homogeneous enhancement of the thickened meninges with leptomeningeal involvement (like solid tissue) (B); T2 sequences: low intensity (C); diffuse weighted imaging with high signal (D); apparent diffusion coefficient map with restricted signal (E).

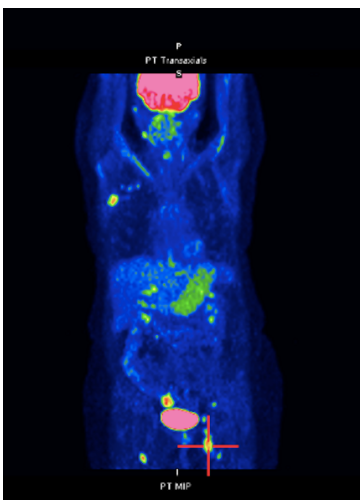


Figure 3. 18 fluorodeoxyglucose-positron emission tomography-computed tomography: hyper fixation areas: right auricular zone, right latero-cervical zone, right axillar area, bilateral iliac area and inguinal-bilateral area.