The Key Role of Splenectomy in Fever of unknown Origin which Resulted to be B-cell primary Splenic Lymphoma.

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Received: 10 April 2023 / Accepted: 2 May 2023 / Published online: 20 July 2023
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Abstract
Background: The term ‘fever of unknown origin’ (FUO) was first introduced by Petersdorf and Beeson in 1961, and it is defined as recurrent fever >38.3°C, lasting for >3 weeks, remaining undiagnosed after 1 week of in-hospital evaluation. The etiologies of classic FUO include mainly infections, malignancies, non-infectious inflammatory diseases, and miscellaneous causes, while some cases remain undiagnosed. Primary splenic lymphoma (PSL) is a rare malignant lymphoma. In many cases, splenectomy is the treatment of choice for massive splenomegaly.

Case presentation: A 54-year-old woman presented with a history of high fever up to 39°C, sweating, fatigue, and weight loss for one month. She had been treated by her family physician with antibiotics (cephalosporin) for 10 days but without improvement. On admission, the patient had palpable splenomegaly but no palpable lymphadenopathy. The patient had increased markers of inflammation. The indicators of autoimmune disease were all negative. Screening for specific infectious diseases and the blood cultures all came out negative. Abdominal computerized tomography (CT) revealed an enlarged spleen. The splenectomy was performed and the spleen was sent for histological analysis. Meanwhile, the patient was subject to a complex treatment. Histological and immunohistochemical analysis confirmed the diagnosis of diffuse large B-cell non-Hodgkin lymphoma with diffuse red pulp infiltration. Afterward, the patient underwent systemic chemotherapy.

Conclusion: We strongly suggest that clinicians should have a high index of suspicion for malignancies in cases with FUO. Sometimes splenectomy can be the key to solving the problem.

Keywords: fever of unknown origin, primary splenic lymphoma, splenomegaly, splenectomy.

Background
The term ‘fever of unknown origin’ (FUO) was first introduced by Petersdorf and Beeson in 1961 based on an analysis of 100 cases, and it was defined as recurrent fever >38.3°C, lasting for >3 weeks, remaining undiagnosed after 1 week of in-hospital evaluation. [1]

The etiologies of classic FUO mainly include infections, malignancies, non-infectious inflammatory diseases, and miscellaneous causes, while some cases remain undiagnosed. [2, 3] Primary splenic lymphoma (PSL) is a rare malignant lymphoma with an incidence of ~1% among patients with non-Hodgkin lymphoma (NHL), although the spleen is involved in approximately half of the cases of Hodgkin’s disease and one-third of NHLs as part
of systemic disease. PSL is a lymphoma that originates in the spleen and is confined to this area for a few months, followed later by its appearance in another location. Massive splenomegaly is indicated by spleen weight exceeding 1000 g and largest spleen dimension greater than 20 cm. [4]

Based on the literature data, we can say that splenectomy is the best solution in massive splenomegaly. Splenectomy is not only a diagnostic procedure, but also a therapeutic choice for splenic lymphoma. [5]

**Case Report**

A 54-year-old woman presented with a history of fever up to 39°C, sweating, fatigue and weight loss for one month. She had been treated by her family physician with antibiotics (cephalosporin) for 10 days but without improvement. On admission the patient had palpable splenomegaly but no palpable lymphadenopathy. The patient had increased markers of inflammation: Fib 656 mg/dl (normal 200-400), ERS= 65 mm/h (normal <16), PCR 57 mg/l (normal <5), LDH 760 U/L (normal 125-220), ALP 289 U/L (normal 40-150) Protein electrophoresis: albumin 51.6% (56-68), alfa1 globulin 4.7% (2-4), alfa2 globulin 15.1% (6-11), beta globulin 11.1% (8-14), gamma globulin 17.5% (9-18). The indicators of autoimmune disease came all negative. Screening for specific infectious diseases including tuberculosis, viral infections such as HIV, cytomegalovirus, Epstein-Barr virus (EBV) was negative. The blood cultures were negative. Abdominal computerized tomography (CT) revealed massive splenomegaly (21cm), lymph nodes in the spleen hilum, without hepatomegaly or other concerns. (Fig 1) Splenectomy was performed, and spleen was sent for histological analysis. Histological and immunohistochemical analysis confirmed the diagnosis of diffuse large B-cell non-Hodgkin lymphoma. The normal tissue structure of the spleen appears to be replaced by a lymphoid cell population (CD45 +) of the centroblastic type with differentiation B (CD20 +, CD79 +); the tumor cells have increased mitotic index, infiltrate the red pulp diffusely causing extensive tumor necrosis; the cells were negative for CKMNF, CD3, CD5, BcL6, BcL2, Cyclin D1, CD30, CD10, CD15, CD23; the cells were positive for CD20, CD79. Ki-67 labeling index was 80-85%. Afterwards the patient underwent systemic chemotherapy.

**Discussion**

We decided to publish this case to show the connection between infectious diseases and other pathologies, and to highlight the importance of the collaboration between the Infectious Diseases Specialist and other Specialists.

Fever is the most important groundwork of the infectious disease specialist’s job, but not always fever is of an infectious origin, as other pathologies might be often hidden behind them. We can say that one of the causes of fever is malignant pathologies. In one of their studies *Stamatis P Efstathiou et al.*, showed that malignancies are one of the causes of FUO in 30.4% of cases. [6]

But also, within malignancies, different pathologies occupy different places. Among the neoplastic causes of FUO, malignant lymphomas are the most common. [7]

Primary Splenic Lymphoma (PSL) is a rare neoplasm of the spleen. The spleen may be the primary site of the lymphoma, or it may be a component of disseminated lymphomas. PSL is generally presented as B cell non-Hodgkin lymphoma. Our patient presented with a history of fever >39°C, sweating, weight loss for one month.

These are signs and symptoms described in literature. The most common presenting symptoms of PSL are fever, malaise, left upper quadrant pain, weight loss and night sweats. [1]

Abdominal computerized tomography (CT) performed on our patient showed massive splenomegaly (21cm), lymph nodes in the spleen hilum, without hepatomegaly or other concerns.

However, we say that the CT does not confirm the diagnosis since splenectomy is what confirms the diagnosis and prevents splenic rupture. This was the best solution since the splenic biopsy has a very high morbidity as a result of procedural hemorrhage or pneumothorax as a procedural complication. In many cases, splenectomy is the treatment of choice for massive splenomegaly. [4]

After the splenectomy procedure, we performed a spleen biopsy that confirmed the diagnosis of diffuse

![Figure 1. Lymph nodes in the spleen hilum](image-url)
large B-cell non-Hodgkin lymphoma. Finally, our patient underwent systemic chemotherapy procedures.

**Conclusion**

We suggest that clinicians should keep a high index of suspicion for malignancy in cases with fever of unknown origin. We can also say that splenectomy can be the key to solving the case although the operative risk in massive splenomegaly is too high.

**List of abbreviations:** FUO - fever of unknown origin; CT – computed tomography; PSL – primary splenic lymphoma; NHL – non-Hodgkin lymphoma

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Availability of data and materials:** Not applicable.

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** We have no sources of funding to declare in this study.

**Authors’ contributions:** EM concepted and drafted the manuscript. AB designed and revised the work. RO participated in the sequence alignment and performed statistical analysis. JP participated in the design of the study and performed the laboratory analysis. LB participated in its coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

**Acknowledgements:** Not applicable.

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