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CLINICAL AND DIAGNOSTIC CHALLENGES IN PRIMARY SPLENIC LYMPHOMAS: WHEN IS SPLENECTOMY NECESSARY TO DIFFERENTIATE SMZL FROM DLBCL?

Natalija Murane[1], Jelena Ivanova[2], Alla Sklevska[2], Jekaterina Aleksejeva[2], Viktors Kozirovskis[1,3], Aldis Pukitis[1,2], Polina Zalizko[1,2]

[1] The Faculty of Medicine and Life Sciences, University of Latvia, Riga, Latvia
[2] Centre of Gastroenterology, Hepatology and Nutrition, Pauls Stradiņš Clinical University Hospital, Riga, Latvia
[3] Center of Oncology, Pauls Stradiņš Clinical University Hospital, Riga, Latvia

Corresponding author's e-mail: muranenatalija@gmail.com

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ABSTRACT

Background: Primary splenic lymphoma (PSL) is a rare form of lymphoproliferative neoplasm, accounting for less than 2% of all lymphomas and approximately 1% of non-Hodgkin lymphomas. While the spleen is often involved in advanced lymphoproliferative disorders, its isolated primary involvement presents significant diagnostic challenges. PSL includes both indolent subtypes, such as splenic marginal zone lymphoma (SMZL), and aggressive forms such as diffuse large B-cell lymphoma (DLBCL).

Case description: We report two cases of PSL with distinct clinical and histological features. The first case involves a 65-year-old male with prior radioiodine treatment for thyroid carcinoma and occupational radiation exposure, who presented with progressive splenomegaly over four years. Splenectomy revealed SMZL characterised by infiltration of small, mature CD20-positive B-cells and a low proliferative index. The patient remains under observation without systemic treatment. The second case concerns a 78-year-old female with a history of breast cancer and hysterectomy, presenting with constitutional symptoms, splenomegaly and diffuse abdominal pain. Imaging demonstrated hypermetabolic splenic lesions and cervical lymphadenopathy. Splenectomy confirmed DLBCL with high Ki-67 index and CD20, BCL6 expression. Systemic chemotherapy with modified rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine and prednisone (R-CHOP) was initiated.

Conclusion: These cases underscore the diagnostic complexity of PSL, highlighting the importance of histopathological confirmation to distinguish between indolent and aggressive subtypes. In patients with isolated splenomegaly and non-specific systemic symptoms, timely evaluation – including imaging and splenectomy – is critical for accurate diagnosis and appropriate management.

KEYWORDS

Spleen marginal zone lymphoma (SMZL), diffuse large B-cell lymphoma (DLBCL), non-Hodgkin lymphoma (NHL), splenomegaly, splenectomy

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LEARNING POINTS

- Unexplained splenomegaly warrants consideration of primary splenic lymphoma in the differential diagnosis, even without lymphadenopathy or classic B symptoms, particularly when detected during abdominal imaging for hepatosplenic evaluation.
- Histopathologic and molecular confirmation is essential, as indolent subtypes (e.g. SMZL) and aggressive subtypes (e.g. DLBCL) may present identically but require fundamentally different treatment approaches.
- PET/CT-guided diagnostic strategy optimises outcomes by enabling accurate staging, identifying the most metabolically active site for biopsy, and informing the need for splenectomy versus direct systemic therapy.

INTRODUCTION

Primary splenic lymphoma (PSL) is a rare type of lymphoproliferative tumour in which lymphocyte transformation occurs primarily in the spleen with further dissemination by lymph ducts. Generally, in 30–40% of all non-Hodgkin lymphoma the spleen is involved[1]. Overall, PSL accounts for less than 2% of all lymphomas and approximately 1% of all NHL[2]. In general, there are few types of splenic lymphoma: indolent types such as splenic marginal zone lymphoma (SMZL) and follicular lymphoma, or more aggressive forms such as diffuse large B-cell lymphoma (DLBCL) or hepatosplenic T-cell lymphoma.

The median age at diagnosis of SMZL is 69 years. The overall age-adjusted incidence is 0.13/100,000 habitants per year. The percentage change in age-adjusted incidence is 4.81%, with most of the patients being white[3]; there is no significant difference between men and women. However, some publications note that men may have a higher incidence of SMZL.

All types of splenic lymphomas mentioned above can be primary located in the spleen. PSL usually is presented with non-specific symptoms: weight loss, weakness, fever, abdominal pain based on splenomegaly; specific symptoms occur with disseminating of the process[2]. Unexplained weight loss is the most common B symptom observed in both clinical cases. Cytopenias are found only in 25% of cases due to hypersplenism[4].

CASE DESCRIPTION

We present two clinically and histologically different cases of PSL, both initially identified through isolated splenomegaly, underscoring the diagnostic complexity and heterogeneity of this rare entity.

Case 1: A 65-year-old male presented with a sudden onset of nausea followed by recurrent episodes of vomiting in September 2020. An abdominal ultrasound revealed splenomegaly. Laboratory investigations demonstrated leukopenia, mildly elevated C-reactive protein and hypoalbuminemia in the free fraction. A contrast-enhanced computed tomography (CT) scan of the abdomen confirmed a splenomegaly measuring 16 cm. Over the subsequent four years (2021–2024), progressive splenic enlargement was observed, reaching 25 cm *(Fig. 1)*. A bone marrow trephine biopsy was performed in 2021 with unremarkable findings. Due to persistent splenic growth and increasing abdominal discomfort, a splenectomy was performed on 23 January 2024.

Histopathological examination of the spleen demonstrated obliteration of the normal architecture with marked hyperplasia of the white pulp due to infiltration by small, mature CD20++ B-lymphocytes. Tumour cells were also identified along the resection margin. Immunophenotyping was consistent with SMZL, characterised by CD5-, CD23-, BCL6- and CD10- expression, with CD138+ plasma cells comprising less than 10% of the cellular population, predominantly located at the periphery of the nodules. These plasma cells were polyclonal with respect to kappa and lambda light chains. The Ki-67 proliferation index was low (<5%).

On 26 February 2024, a positron emission tomography/computed tomography (PET/CT) scan was performed, revealing at least four additional splenic remnants located in the left upper quadrant. One of these remnants demonstrated moderate hypermetabolic activity, corresponding to a Deauville score of 3 *(Fig. 2)*.

On 27 February 2024, the patient was admitted to the internal medicine department due to persistent low-grade fever. Laboratory tests revealed elevated inflammatory

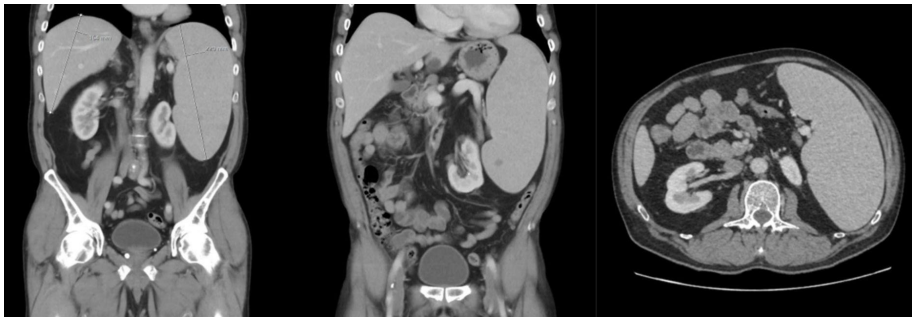


Figure 1. Case 1. Computed tomography scan demonstrating marked splenomegaly. The craniocaudal spleen length measures 25 cm.

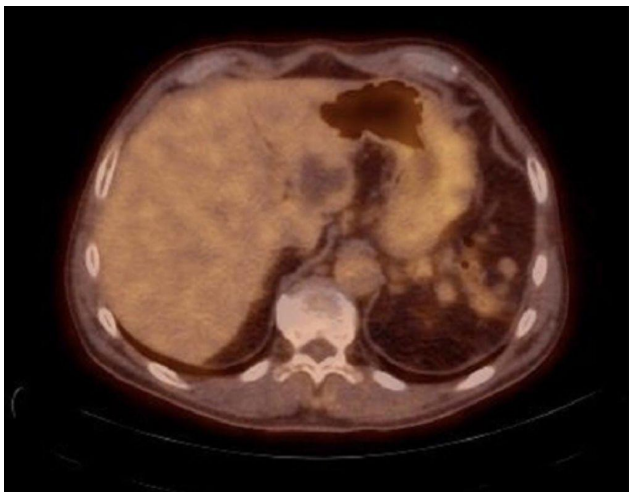


Figure 2. Case 1. Post-operative positron emission tomography/computer tomography scan showing residual splenic tissue with mild hypermetabolism (Deauville score 3).

markers. Respiratory viral infections were excluded, and blood cultures were negative. Upper gastrointestinal endoscopy (esophagogastroduodenoscopy) revealed a small, healing ulcer in the antral region, grade A reflux oesophagitis and suspected Barrett's oesophagus. Histopathological examination confirmed chronic active gastritis with intestinal metaplasia (10–15%) and mild glandular atrophy. Biopsies from the gastroesophageal junction revealed intestinal metaplasia with stromal infiltration by chronic inflammatory cells, consistent with Barrett's oesophagus.

The patient remains under close follow-up by haematology and gastroenterology specialists with the intent to start specific treatment in case of stage IA indolent lymphoma rapid progression or symptoms. His medical history is notable for several potential risk factors for lymphoproliferative disorders. He worked as a construction worker with occupational exposure to various environmental risk factors. A family history of haematological malignancy is present, as his father had an unspecified haematological disease. Additionally, the patient has a history of potential radiation exposure, having served in military operations near nuclear weapons facilities close to the Chernobyl disaster site. In 2018, he was diagnosed with follicular thyroid carcinoma, which was surgically resected, followed by radioactive iodine (I-131) therapy.

Case 2: A 78-year-old female was hospitalised in October 2023 due to progressive weakness, unintentional weight loss of 10 kg over six months, diffuse abdominal pain and lower back pain. Physical examination and laboratory tests revealed mild microcytic, hypochromic anaemia. Abdominal ultrasonography demonstrated a splenomegaly measuring 13.4 × 5.7 cm.

On 5 October 2023, contrast-enhanced CT of the chest and abdomen confirmed a splenomegaly (14.5 × 6.2 cm) with smooth contours. Several sectoral contrast defects were identified in the spleen, the largest located in the middle third, although no discrete focal lesions were detected. The thoracic organs appeared unremarkable, with no evidence of malignancy in the thorax or mediastinum. Further haematological evaluation, including bone marrow trephine biopsy, revealed reactive changes without evidence of lymphoproliferative disease. Upper and lower gastrointestinal endoscopies were unremarkable. The patient was discharged with a diagnosis of anaemia of unknown aetiology, and splenomegaly.

The patient's medical history was notable for bilateral breast cancer, treated with surgical resection in 2006 and 2012 followed by chemotherapy, as well as a hysterectomy with adnexectomy performed in 2010.

As her clinical symptoms progressed, the patient was re-hospitalised on 23 November 2024, following referral by her family physician. A repeat contrast-enhanced abdominal CT scan revealed increased spleen size (12 × 7.5 × 17.5 cm, estimated volume ~800 ml), with heterogeneous contrast enhancement and subcapsular content up to 2.7 cm in thickness *(Fig. 3)*. A 3.0 cm accessory spleen was visualised at the splenic hilum. No significant pathological findings were noted in other abdominal organs. Thoracic imaging revealed a left-sided pleural effusion up to 2.0 cm in thickness *(Fig. 4)*. Laboratory tests showed persistent microcytic anaemia,

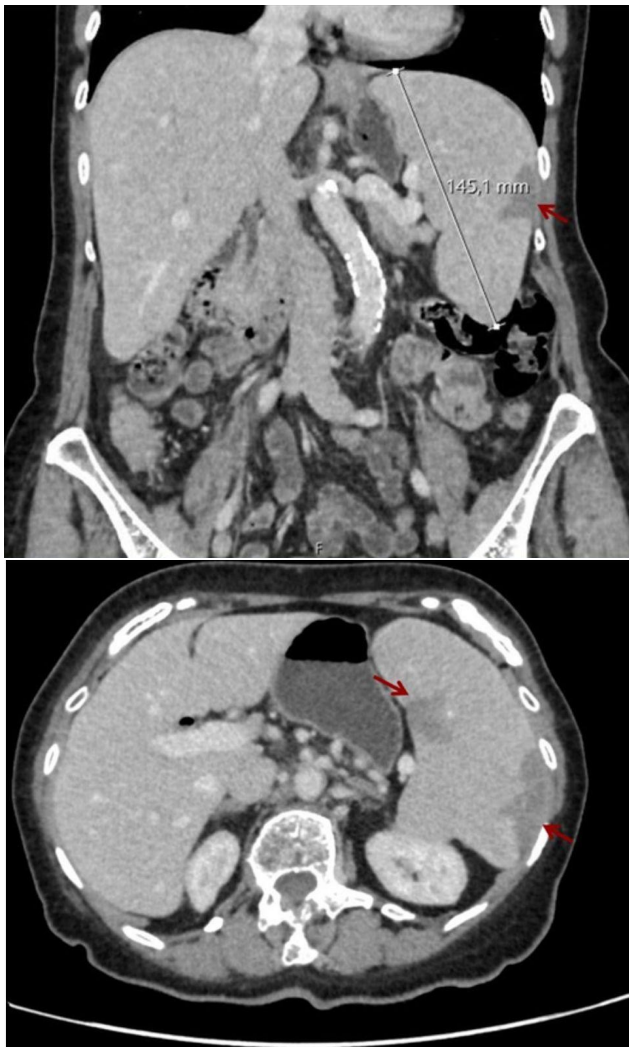


Figure 3. Case 2. Computed tomography scan of the abdomen demonstrating splenomegaly with subcapsular collection and heterogeneous contrast enhancement.

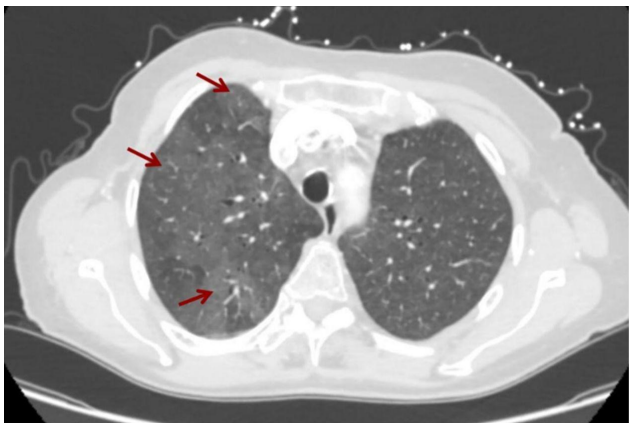


Figure 4. Case 2. Computed tomography scan of the thorax demonstrating left-sided pleural effusion.

mild lymphopenia and negative results for autoantibodies, viral and bacterial infections. Comprehensive investigations, including echocardiography, abdominal MRI, skeletal scintigraphy and transvaginal ultrasonography did not reveal evidence of malignancy.

Due to ongoing diagnostic uncertainty, the patient underwent PET/CT on 14 December 2023. The scan demonstrated splenomegaly with diffuse hypermetabolic activity consistent with lymphoproliferative disease, corresponding to a Deauville score of 5. Additionally, two hypermetabolic cervical lymph nodes were identified on the right side: one in the IIB/III region (Deauville 5) and a smaller, mildly suspicious node in region IIA (Deauville 3). A slightly hypermetabolic lymph node was observed in the precarinal mediastinum (Deauville 3), possibly reactive to the pleural effusion *(Fig. 5)*. No abnormal hypermetabolic activity was detected elsewhere, including the skeletal system.

A splenectomy was performed on 28 December 2023. Histopathological analysis revealed complete effacement of normal splenic architecture with massive white pulp infiltration by medium to large CD20++ B-cells. Immunophenotyping was consistent with DLBCL, characterised by CD5-, Cyclin D1-, CD138-, BCL6+ (~10%), and Ki-67 proliferation index ranging from 20% to 60%; CD23 expression was absent. Plasma cells exhibited polyclonal kappa and lambda light chain expression. Areas of extensive necrosis with eosinophilic homogeneous masses and zones of demarcation were also observed.

A multidisciplinary oncology board recommended induction therapy with R-CVP regimen (rituximab, cyclophosphamide, vincristine, prednisone) for this stage IIIB aggressive lymphoma due to patient age and potentially reached cumulative doxorubicin dose, received previously during treatment for breast cancer. Six cycles were received with a clinical and radiological improvement of lymphoma signs and symptoms. Grade 1 rituximab-induced pneumonitis developed after the fifth cycle, which required a short course of corticosteroids and omission of rituximab in the last cycle. On 8 August 2024, post-treatment PET/CT scan was performed, revealing complete metabolic remission. The patient is on follow-up now without any signs of relapse.

DISCUSSION

PSLs comprise a rare and heterogeneous category of lymphoproliferative malignancies, representing <2% of all lymphomas and approximately 1% of non-Hodgkin lymphomas[5]. While splenic involvement is a frequent manifestation in advanced stages of various haematologic malignancies, exclusive primary involvement of the spleen as the initial site of disease is rare and presents substantial diagnostic complexity[6]. The two cases presented in this report illustrate the clinical variability of PSLs and underscore the importance of histopathological confirmation to guide appropriate management.

The first case, diagnosed as SMZL, exemplifies the indolent spectrum of PSLs. SMZL is a low-grade B-cell lymphoma typically presenting with isolated splenomegaly, cytopenia and minimal systemic symptoms. In line with existing literature, our patient exhibited progressive splenomegaly over several years, without lymphadenopathy or aggressive clinical features. Splenectomy served both diagnostic and therapeutic purposes, and subsequent observation without systemic treatment was deemed appropriate, reflecting the natural history and favourable prognosis of SMZL[7].

In contrast, the second case was diagnosed as DLBCL with massive involvement of the spleen, an aggressive entity often associated with systemic symptoms, high metabolic activity on PET imaging and a high proliferative index. This patient presented with constitutional symptoms and rapid disease

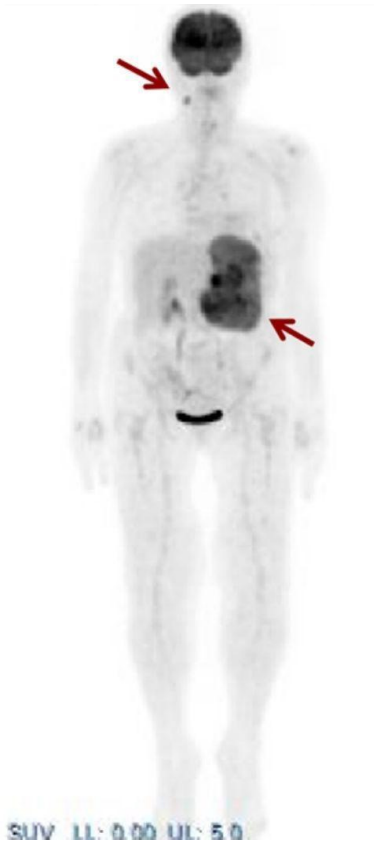


Figure 5. Case 2. Positron emission tomography/CT demonstrating splenomegaly with diffuse hypermetabolic activity (Deauville 5) and right cervical lymphadenopathy (Deauville 5 and 3).

progression, ultimately requiring systemic chemotherapy following splenectomy. Immunohistochemical analysis demonstrating CD20 and BCL6 positivity, in conjunction with a Ki-67 proliferation index of up to 60%, substantiated the high-grade biological behaviour of the disease[8]. Importantly, the lack of disseminated nodal involvement highlights the potential for DLBCL to present as isolated splenic disease, underscoring the pivotal role of PET/CT in precise staging and phenotypic characterisation.

These cases contribute to the existing literature by offering a comparative perspective of two histologically distinct PSL subtypes with overlapping clinical presentations. The initial radiologic and clinical findings in both patients were non-specific, underscoring the necessity of tissue diagnosis. Moreover, these cases illustrate that isolated splenomegaly necessitates a comprehensive diagnostic approach, incorporating haematologic assessment, advanced imaging modalities and, in a substantial proportion of instances, therapeutic splenectomy.

This report highlights the clinical significance of distinguishing between indolent and aggressive forms of PSL. While SMZL may be managed conservatively following splenectomy, DLBCL typically necessitates prompt systemic therapy[9]. For internists and general physicians, these cases underscore the importance of maintaining a high index of suspicion for haematologic malignancy in patients presenting with unexplained splenomegaly and subtle systemic symptoms. Early recognition and referral can significantly impact diagnostic accuracy and therapeutic outcomes. Historically, splenectomy was the principal diagnostic and therapeutic approach for splenic lymphomas; however, advances in high-resolution imaging, flow cytometry and molecular diagnostics have largely replaced the need for invasive surgical procedures for diagnostic or staging purposes.

Data from splenic lymphomas diagnosed in the United States between 2004 and 2013 demonstrate a marked decline in splenectomy utilisation, although surgery remains frequent, with rates ranging from 49% in SMZL to 77% in follicular lymphoma, including 48% of patients with advanced-stage disease. More than half of splenectomies were performed for diagnostic purposes, and a considerable proportion of patients – ranging from 29% in DLBCL to 85% in SMZL – did not receive chemotherapy following diagnostic splenectomy. Among patients with DLBCL, omission of chemotherapy after diagnostic splenectomy was associated with significantly inferior survival, a finding not observed in other histologic subtypes such as mantle cell and T-cell lymphomas, despite their typically disseminated presentation and standard indication for chemotherapy. Overall survival did not significantly differ between splenectomised and non-splenectomised patients.

CONCLUSION

Despite a decline in use, nearly half of patients with splenic lymphomas still undergo splenectomy, highlighting the need for accurate non-invasive diagnostics. Given the frequent disseminated presentation and lack of survival benefit, its role should be reconsidered when less morbid options exist. In splenic DLBCL, standard chemotherapy is essential regardless of surgery, whereas in SMZL or follicular lymphoma, diagnostic splenectomy alone may suffice. In mantle cell and T-cell lymphomas, prognosis remains poor and unaffected by splenectomy, warranting further research[10].

In another study, splenectomy proved valuable in selected cases of fever of unknown origin and unexplained splenomegaly, particularly when exhaustive diagnostic investigations had been completed beforehand. The procedure most frequently yielded a diagnosis of lymphoproliferative disorders, with DLBCL being the predominant finding, sometimes confined to the spleen. Analysis of preoperative assessments emphasised the critical role of comprehensive diagnostic work-up prior to surgery. The study also highlighted the utility of PET/CT and complete haematologic evaluation in these scenarios, proposing a diagnostic algorithm to guide clinical decision-making before undertaking splenectomy.

An important diagnostic distinction between SMZL and DLBCL lies in their characteristic histopathologic and clinical presentations. In SMZL, tumour infiltration is frequently accompanied by the formation of reactive lymphoid follicles within the spleen, lymph nodes or bone marrow. This reflects the ability of marginal zone B-cells to induce germinal centre development via transport of immune complexes to follicular dendritic cells – a pattern not typically encountered in DLBCL[11]. In contrast, DLBCL demonstrates diffuse effacement of the normal architecture by sheets of large atypical lymphoid cells with vesicular nuclei, prominent nucleoli, abundant cytoplasm and a high mitotic index, without the preservation of follicular structures[12].

Bone marrow involvement is almost invariably present in SMZL and may be challenging to identify on routine morphologic sections, warranting careful review by experienced haematopathologists in cases lacking overt infiltration[13].

In DLBCL, bone marrow involvement occurs less frequently and usually in advanced stages. Peripheral blood involvement is common in SMZL, often with small numbers of neoplastic B-cells exhibiting villous morphology characterised by cytoplasmic projections at one pole and relatively abundant cytoplasm; such findings are rare in DLBCL except in leukaemic variants[14].

Molecularly, SMZL is frequently associated with chromosome 7q deletion, recurrent NOTCH2 mutations and p53 inactivation, while DLBCL exhibits subtype-specific alterations, including MYD88 and CD79B mutations in ABC-type and EZH2 mutations or BCL2 translocations in GCB-type, with frequent BCL6 rearrangements[15].

In summary, SMZL can often be diagnosed with a high degree of confidence through the integration of clinical features, immunophenotyping and histologic evaluation of bone marrow and peripheral blood specimens, thereby

reducing the need for diagnostic splenectomy. Conversely, DLBCL diagnosis requires excisional biopsy of an involved lymph node or extranodal site to obtain sufficient tissue for morphologic, immunohistochemical and molecular characterisation, given its aggressive and heterogeneous nature.

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