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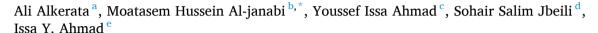
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Case report

Primary breast lymphoma: A rare case report



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ABSTRACT

Case presentation: This case report discusses a 60-year-old female patient presenting with a primary breast lymphoma, specifically diffuse large B-cell lymphoma. The patient had no personal history of breast cancer but exhibited a painless, palpable mass in the left breast with axillary lymphadenopathy.

Clinical discussion: Diagnostic challenges in distinguishing PBL from primary breast carcinoma are addressed, emphasizing the importance of considering PBL in cases of rapidly enlarging breast masses. Radiological examinations, including mammography and ultrasound, play a crucial role in diagnosis, and excisional biopsy with immunohistochemical staining is essential for accurate histopathological subcategorization.

Conclusion: The presented case underscores the rarity of PBL in the Middle East and highlights the diagnostic and classification challenges, emphasizing the central role of accurate techniques in guiding treatment decisions.

1. Introduction

Primary breast lymphoma (PBL) is an exceptionally rare neoplasm, with a prevalence ranging from 0.04 % to 0.7 %, primarily due to the scarcity of lymphoid tissue in the breast [1]. It constitutes less than 2 % of extranodal non-Hodgkin lymphomas (NHLs) and under 0.1 % of breast cancers [1,2]. Diagnosing PBL is challenging because it is rare for patients to present with both a breast mass and widespread adenopathy, complicating the differentiation from primary breast carcinoma with concurrent lymphoma [3].

PBL can originate as a primary tumor or involve the breast secondarily as part of a metastatic process [4]. It is notably more aggressive and has a poorer prognosis compared to extranodal NHLs at other sites, such as the gastrointestinal tract [3]. Treatment approaches for PBL are not well-defined and are typically adapted from protocols for other extranodal lymphomas. Recent studies recommend radiation and systemic therapies over surgery, which is generally reserved for obtaining a histologic diagnosis to guide definitive treatment [5–7]. Radical mastectomy has no added benefit in managing PBL [5]. Additionally, local

breast and central nervous system (CNS) recurrences are significant challenges after standard R-CHOP treatment for PB-DLBCL patients [8].

In this report, we describe a unique case of PBL in a 60-year-old female, identified incidentally during histopathological evaluation.

This case report has been reported in line with SCARE Criteria [9].

2. Case presentation

We present a 60-year-old female with a 5-year history of hypertension and infertility. The patient has no personal history of breast cancer, but three of her brothers died from malignancies (leukemia, prostate, and lung cancer). There are no inflammatory lesions present.

The patient presented to the surgical department with a gradually enlarging lump in the left breast over the past year, without associated weight loss. Laboratory tests were normal. On examination, she had a painless, palpable mass in the upper lateral quadrant of the left breast, measuring 34.5×33.5 mm. The mass was hard, mobile, and non-adherent to the skin or underlying tissue. Additionally, there was a suspicious axillary lymphadenopathy.

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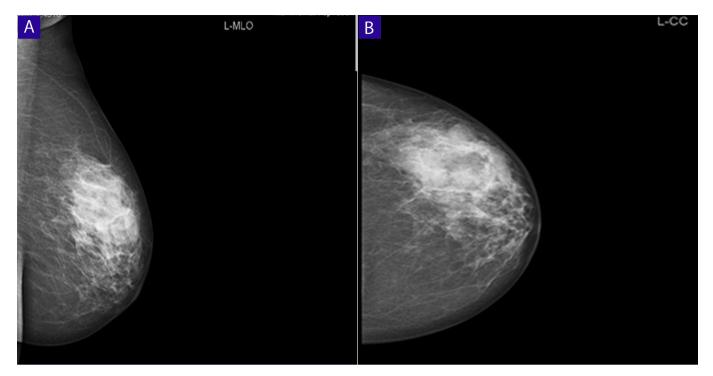


Fig. 1. A Mammogram images (A and B) show a nodular lesion with lobulated contours, measuring 44.5×24.5 mm.

A core needle biopsy revealed large atypical lymphoid cells, most probably indicating diffuse large B-cell lymphoma. Mammography described the lesion as a nodular mass with lobulated contours, measuring 44.5×24.5 mm [Fig. 1]. Ultrasound showed a hypoechoic, heterogeneous nodule with lobulated and ill-defined contours, along with multiple ipsilateral axillary adenopathies, the largest measuring 15 mm. The lymph node biopsy was performed and revealed the presence of atypical lymphocytes. Surgical excision of the mass was performed, including a small margin of surrounding healthy tissue, with an operative time of 90 min. No intraoperative complications were noted.

Microscopic examination of the excised lesion revealed a diffuse infiltrate of large atypical lymphoid cells [Fig. 2]. Immunohistochemical analysis showed positive staining for CD20, CD45, CD5, CD10, MUM1, Bcl2, and BCL6, with a high proliferation index indicated by Ki-67. The analysis was negative for the cytokeratin cocktail [Figs. 3, 4, and 5].

The diagnosis of diffuse large B-cell lymphoma (DLBCL) was initially made based on the core needle biopsy and was confirmed by immuno-histochemical analysis after the surgical excision of the mass.

The immediate postoperative course was uneventful, and the patient did not require blood transfusions. Follow-up included positron emission tomography (PET) scans, which confirmed no extraganglionic involvement. A staging CT scan found no additional lesions beyond those already described. The patient was then referred to an oncology center. Adjuvant treatment consisted of six cycles of R-CHOP chemotherapy, followed by consolidative radiation therapy and five doses of intrathecal methotrexate as a CNS prophylactic measure.

3. Discussion

Primary breast lymphoma (PBL) is a rare neoplasm that clinicians managing breast carcinomas must recognize to differentiate its clinical presentation, management, and prognosis from breast carcinoma cases [10]. Malignant lymphoma in the breast is uncommon and can be categorized as either primary breast lymphoma (PBL) or secondary breast lymphoma (SBL) [11]. PBL is particularly rare in the Middle East, with studies from Tunisia, Iran, and Morocco highlighting its infrequency [12–14]. For example, a case report from Sudan noted the first

documented instance of PBL in the country [15]. These observations underscore PBL's rarity on a global scale.

PBL is characterized by breast lymphoma without systemic disease involvement, primarily B-cell lymphoma, comprising up to 50 % of PBL cases, with some being follicular lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, or Burkitt lymphoma [10-12]. The most prevalent type of PBL is diffuse large B-cell lymphoma (DLBCL), accounting for 60-85 % of cases [16].

The age incidence of PBL varies widely, occurring in individuals ranging from 9 to 85 years, with the highest frequency observed in the sixth decade. While the majority of cases affect females, a few instances have been documented in males [17]. PB DLBCL has a significant risk of relapse, including in the CNS. Studies have shown that CNS relapse in PB-DLBCL patients can substantially impact prognosis, with a 5-year overall survival rate of 84.7 % and a progression-free survival rate of 69.6 %. Interestingly, the risk of CNS relapse in PB-DLBCL can be reduced by prophylactic high-dose methotrexate (HD-MTX), especially in patients with MYD88 and/or CD79B mutations, where none of the patients who received HD-MTX experienced CNS relapse [18]. However, despite the effectiveness of HD-MTX in reducing CNS relapse risk in PB-DLBCL, the incidence of CNS relapse remains a significant concern, emphasizing the need for further research and optimized treatment strategies to improve outcomes in these patients.

Moving on to manifestations of PBL, it typically presents as a rapidly enlarging, painless, palpable, solitary lump that is relatively movable, with or without associated axillary lymph node enlargement on the same side, resembling breast carcinoma [11]. However, it's important to consider PBL in the differential diagnosis of rapidly enlarging breast masses [10]. PBL can be classified based on presenting symptoms into type A (unusual symptoms) and type B (fever, night sweats, 10 % weight loss within six months) [10]. Our patient presented with a painless, palpable mass that had gradually enlarged over the past year without weight loss. The lump was hard, mobile, and non-adherent to the skin or underlying tissue.

PBL predominantly affects a single breast, with a higher incidence in the upper right quadrant, and approximately 1 % to 14 % of PBL cases are characterized by bilateral breast lymphomas [10]. Numerous studies

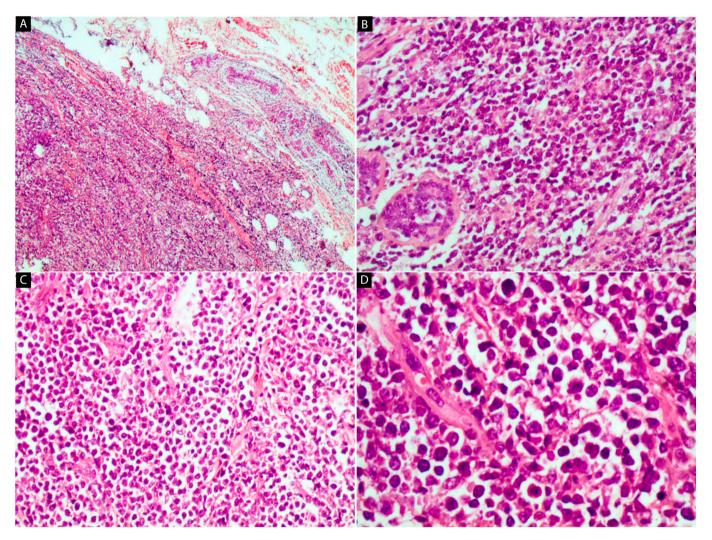


Fig. 2. Hematoxylin and eosin stain (A-D). Microscopic images of mass. (A and B) The low-power magnification shows complete effacement of normal tissue architecture by a diffuse infiltrate of large atypical lymphoid cells ($40 \times$ and $100 \times$). (C and D) The high-power magnification shows large, atypical cells with vesicular chromatin, prominent nucleoli, and atypical mitotic figs. ($200 \times$ and $400 \times$).

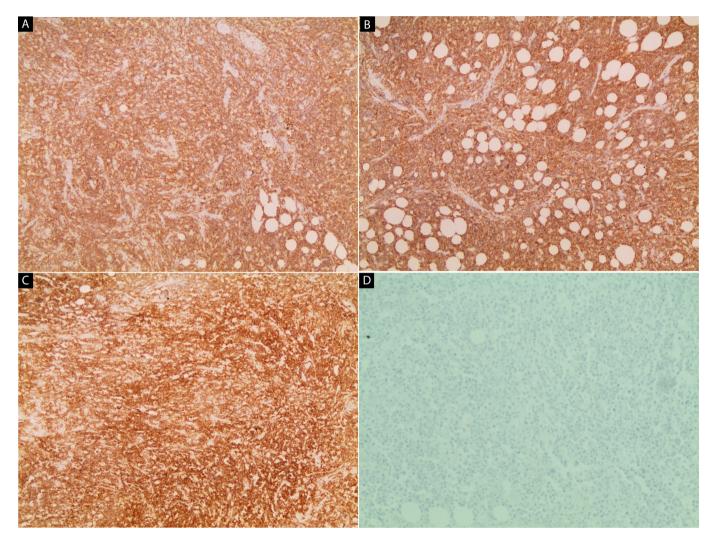


Fig. 3. Immunohistochemistry images (A-D). (A and B) Tumor cells are positive for CD20 ($40\times$). (C) Tumor cells are positive for CD45 ($100\times$). (D) Tumor cells are negative for the cytokeratin cocktail ($40\times$).

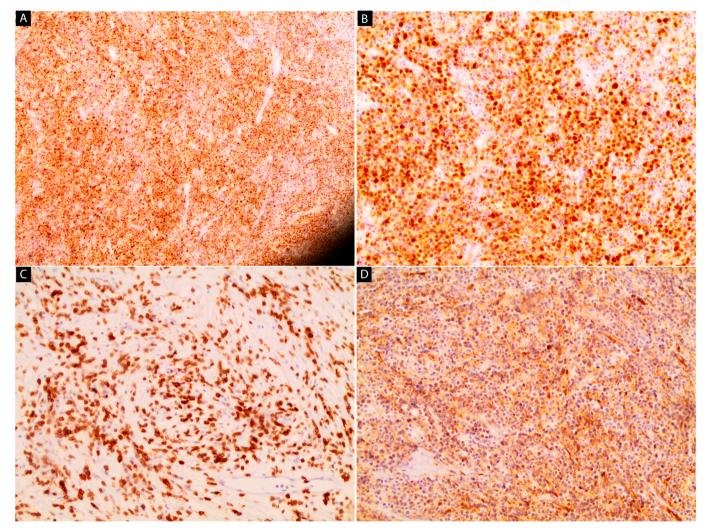


Fig. 4. Immunohistochemistry images (A-D). (A, B) Tumor cells show strong positivity for MUM-1 ($40 \times$ and $100 \times$). (C) Tumor cells are positive for CD5 ($100 \times$). (D) Tumor cells are positive for CD10 ($100 \times$).

have shown a higher occurrence of PBL on the right side [17]. Sixty percent of the patients displayed localization in the superior outer quadrant [17]. According to Decosse et al. [10], 8 out of 14 cases exhibited a preference for this specific region of the breast. However, in our patient, the lump was detected in the upper lateral quadrant of the left breast.

The diagnostic procedure for PBL involves radiological examinations (such as mammography, ultrasonography, magnetic resonance imaging, and positron emission tomography), fine-needle aspiration cytology (FNAC), and the use of immunohistochemical markers [10]. Mammography results can range from distinct nodules with irregular margins to multiple thickened areas resembling dysplastic lesions, or observations like a diffuse increase in breast density along with skin thickening [19]. In our case, the lesion was described as a nodular lesion with lobulated contours. The most common mammography findings for PBL typically involve the presence of a solitary, reasonably well-defined, non-calcified mass. PBL masses less frequently exhibit features such as microcalcifications, spiculations, irregular margins, or alterations in the tissue architecture in the vicinity [11]. In a study conducted by Sabate et al., 12.5 % of PBL masses appeared well-defined, resembling benign lesions [20].

Ultrasound with color-Doppler is often the initial imaging method due to its non-invasive nature and its capability to differentiate between benign and malignant breast lesions in most instances [20]. On ultrasound, PBL typically presents as a solid oval or round mass with

indistinct boundaries and is often hypervascular, with a hypoechoic appearance in 87 % of cases. Posterior acoustic enhancement is observed in 52–75 % of the masses, and hypervascularity in 55–64 %. Margins with spiculation or calcifications are infrequently detected [12]. In our case study, the lesion corresponded to a hypoechoic, heterogeneous nodule with lobulated and ill-defined contours and showed multiple ipsilateral axillary adenopathies. The imaging characteristics of PBL lack specificity and bear similarities to those of breast cancer, with no single imaging finding unique to the condition [11].

In 1972, Wiseman and Liao introduced criteria for PBL diagnosis: the presence of sufficient tissue specimen for pathological analysis, absence of a prior diagnosis of an extramammary lymphoma, a close anatomical association between mammary tissue and lymphomatous tissue, and an absence of simultaneous widespread disease (except for ipsilateral axillary nodal involvement) [11]. Both aspiration biopsy and excisional biopsy have been employed to confirm the diagnosis of PBL, with the latter being preferred for more accurate histopathological subcategorization [17]. Given the non-specific nature of breast lymphoma symptoms, the primary method for diagnosing PBL relies on histopathological biopsy and immunohistochemical staining [16]. In our case, malignant lymphoid cells were positive for the B-cell markers CD20 and negative for the cytokeratin cocktail. It is imperative to establish a differential diagnosis for PBL, which is critical for understanding its typing and staging based on pathological findings.

It is essential to note that PB DLBCL exhibits unique genetic subtypes

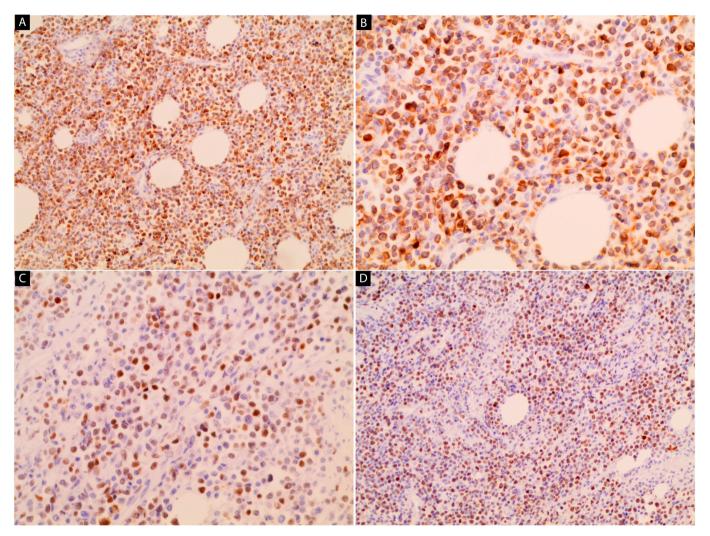


Fig. 5. Immunohistochemistry images (A-D). (A and B) Tumor cells are positive for Bcl-2 ($40\times$ and $100\times$). (C) Tumor cells are positive for Bcl-6 ($100\times$). (D) Ki-67 proliferation rate is 65 % ($100\times$).

and molecular features compared to DLBCL in other primary organs. Studies have shown that breast DLBCL presents a distinct mutational profile with high frequencies of MYD88L265P, CD79B mutations, and CDKN2A/B loss, resembling DLBCL of immune-privileged sites [21]. Furthermore, genetic classification algorithms like LymphPlex have identified specific subtypes within DLBCL, such as EZB-like and ST2like, each with its own biological signature and clinical relevance [22]. Additionally, alternative splicing patterns have been observed in DLBCL subtypes, with BN2 and MCD subtypes showing significantly different exon inclusion levels compared to other subtypes [23]. These findings highlight the importance of molecular subtyping in understanding the heterogeneity of DLBCL, especially in PBL cases, and may have implications for targeted therapeutic approaches. Accurate classification of these tumors can be achieved by discerning their origin from immune tissues, whether they originate from the hematopoietic lymphatic or epithelial systems. Furthermore, the assessment and management of lymphomas have seen significant advancements, driven by the expanding database on gene expression patterns and protein expression [10].

Advances in therapeutic strategies and targeted therapies have significantly improved outcomes for patients with PB-DLBCL. Treatment for PB-DLBCL often involves a combination of rituximab-based chemotherapy, intrathecal methotrexate injection, and radiotherapy, with surgery being an option in some cases [24]. Recent advancements in DLBCL therapies include precision-guided treatments based on gene

expression profiling and next-generation sequencing, allowing for more precise subentity classification and targeted therapy based on somatic mutations [25]. Additionally, newer treatments such as CAR-T cell therapy targeting CD19, and other agents like polatuzumab, selinexor, and tafasitamab plus lenalidomide, have shown potential to improve outcomes for patients with B-cell malignancies [26]. These innovations aim to decrease reliance on traditional chemotherapy, reduce adverse effects, and improve cure rates through personalized and targeted therapies.

Primary breast lymphoma in the Middle East is a rare and challenging condition, with limited data available due to its rarity. Studies from the Salah Azaiez Institute of Oncology in Tunisia and the National Institute of Oncology in Rabat, Morocco, highlight the complexity of this disease, emphasizing the importance of tailored treatment approaches. While surgery is not recommended, a combination of chemotherapy and possibly radiotherapy has shown promising results in managing PBL. The prognosis remains poor, with factors like age, stage at diagnosis, and histological subtype influencing survival rates. Additionally, cases of bilateral PBL have been reported, showcasing the diverse presentations of this malignancy in the region [12,14,27]. See Table 1.

4. Conclusion

In conclusion, we report a case of primary lymphoma of the breast a rare disease and the subtype is diffuse large B-cell lymphoma

International Journal of Surgery Case Reports 122 (2024) 110120

Table 1 Comparative Analysis of Protarian Lymphoma Cases in the Middle East and Current Study

Case characteristics	Current study	Case 1 (Binesh et al. [17], 2013)	Case 2 (Hammood et al. [28], 2022)	Case 3 (Topuz et al. [29], 2023)	Case 4 Mohamed Ali [16], 2017)	Case 5 (Simsek et al. [30], 2022)	Case 6 (Poureisa et al., [27], 2013)	Case 7 (Bozkaya et al. [31], 2019)	Case 8 (Harb et al. [32], 2019)	Case 9 (Vardar et al. [33], 2005)	Case 10 (Jabbour et al. [9], 2016)
Country/ Region	Syria	Iran	Iraq	Turkey	Sudan	Turkey	Iran	Turkey	Egypt	Turkey	Qatar
Age of patient Gender Subtype of Lymphoma	60 years Female Diffuse large B- cell lymphoma	48 years Female Diffuse large B-cell lymphoma	55 years Female Diffuse large B- cell lymphoma	40 years Female Diffuse large B-cell lymphoma	56 years Female Diffuse large B- cell lymphoma	57 years Female Diffuse large B- cell lymphoma	16 years Female Diffuse large B- cell lymphoma	82 years Male B-cell lymphoma with plasmacytic differentiation	56 years Female Diffuse large B-cell lymphoma	40 years Female Diffuse large B-cell lymphoma	43 years Female Diffuse large B-cell lymphoma
Presenting Symptoms	Painless palpable mass in the left breast, axillary lymph adenopathy	Palpable mass in the left breast, no previous breast nodules, skin changes, or nipple retraction	Right breast mass for 4 months, no family history of cancer	Palpable mass in the right breast, no fever, weight loss, or night sweats	Central mass in the right breast, no weight loss, excessive sweating, or fever	Palpable mass in the right breast, later diagnosed with mucinous carcinoma in the left breast	Bilateral breast masses, dyspnea, CNS involvement	Bilateral painless breast masses, no fever, weight loss, or night sweats	Right breast lump, no constitutional symptoms	Bilateral palpable masses and hypoechoic masses were detected on ultrasonography.	Left breast lump, painless, rapidly increasing in size
Diagnostic Methods	Mammography, ultrasound, core needle biopsy, immune- histochemical staining	Ultrasound, excisional biopsy, immune- histochemistry (CD45+, CD20+, CD3-, pan- cytokeratin-)	Ultrasound, mammography, core needle biopsy, histopathology	18F-FDG PET/CT, excisional biopsy	Tru-cut biopsy, immune- histochemistry, CT chest/ abdomen/ pelvis, bone scan	Tru-cut biopsy, immune profile (CD20+), PET- CT scan	Fine needle biopsy, CT scan, MRI, CNS examination		Mammography, ultrasonography, true cut needle biopsy, immune-histochemistry	Fine-needle aspiration biopsy, incisional biopsy, immunohistochemistry (CD20+, CD45+, pan- cytokeratin-)	CT scan, PET, core needle biopsy, immunohistochemistry
Treatment Given	Surgical excision, R- CHOP chemotherapy, radiation therapy, intrathecal methotrexate	R-CHOP chemotherapy, intrathecal methotrexate, radiotherapy	Modified radical mastectomy	Combination chemotherapy	Surgery, chemotherapy (R-CHOP), radiotherapy	R-CHOP chemotherapy, radiotherapy, anastrozole for mucinous carcinoma	Chemotherapy, intrathecal methotrexate, hydrocortisone	R-CHOP chemotherapy	Combination chemotherapy (R- CODOX/IVAC), planned for adjuvant radiotherapy and chemotherapy	CHOP chemotherapy	Combination chemotherapy (R- CODOX/IVAC), radiotherapy
Outcome	No extra- ganglionic involvement, remission status	No evidence of residual disease at the 15-month follow-up	Referred to a hematological center for further management	Complete regression of the disease after chemotherapy	No evidence of disease 2 years after treatment	Remission at 6 years for DLBCL and 5 years for mucinous carcinoma	Death due to severe cranial involvement after 17 months	Bilateral masses disappeared after two cycles of chemotherapy	Favorable radiological response after chemotherapy	Alive with no evidence of recurrence for 2 years	Remission status, radiologically favorable response
Unique Aspects	Emphasizes diagnostic and classification challenges in PBL	Hypoechoic mass with microcalcification, first reported case from Iran	Suspicious mass initially thought to be invasive mammary carcinoma	Isolated mass with increased FDG uptake, no other pathological FDG uptake in the body	The first reported case of PBL in Sudan	The first case of	Bilateral primary breast lymphoma with multi-organ involvement in a teenage girl	breast	Diagnosis confirmed by immunohistochemistry, treatment avoided unnecessary mastectomy	Bilateral primary non- Hodgkin lymphoma, rare bilateral involvement	Non-germinal B-cell type, multiple extranodal presentations

representing one of the very few cases in our region in the Middle East. Furthermore, diagnosing and classification of this unusual entity pose a formidable challenge and have a central role in guiding treatment options and evaluating the impact of adjuvant radiotherapy. However, with the right and most accurate techniques like excisional biopsy and immunohistochemical examinations, we could validate the diagnosis.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Consent for publication

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

Ethical approval

No ethical approval was needed for this case report.

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Author contribution

Ali Alkerata: study design, data analysis, and writing.

Moatasem Hussein Al-janabi: study design, data collections, data analysis, and writing.

Youssef Issa Ahmad: study design, and writing. Sohair Salim Jbeili: performed surgery. Issa Y. Ahmad: in reviewing the manuscript.

Guarantor

Issa Y. Ahmad.

Research registration number

Not applicable.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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