

A Case of Transformation of Primary Cutaneous Follicle Center Lymphoma to Diffuse Large B-Cell Lymphoma Involving the Parotid Gland and Cervical Lymph Nodes

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Conflict of interest: None declared

Patient: Male, 40
Final Diagnosis: Primary cutaneous follicular lymphoma
Symptoms: Scalp mass
Medication: —
Clinical Procedure: Radiation
Specialty: Oncology





Objective: Rare co-existence of disease or pathology
Background: Transformation of primary cutaneous follicle center lymphoma (PCFCL), a low-grade B-cell non-Hodgkin lymphoma (NHL), into a high-grade NHL is rare with uncertain prognosis and treatment. A case is reported of a 40-year-old man who presented with a scalp mass that was diagnosed histologically as PCFCL. Imaging of the head and neck identified diffuse large B-cell lymphoma (DLBCL) involving the parotid gland and cervical lymph nodes, which responded well to radiation therapy.

Case Report: A 40-year-old African American man presented with a two-year history of a progressively enlarging scalp mass that measured 10.5×7.1×6.6 cm. Histology showed a low-grade lymphoma with a follicular pattern. Immunohistochemistry was positive for B-cell markers and Bcl-6, consistent with a diagnosis of PCFCL. Computed tomography (CT) identified a 4.9×3.7×3.4 cm mass in the left parotid gland with bilateral cervical lymphadenopathy that had been present for the previous two or three months. The diagnosis of DLBCL was made on histology from a needle biopsy. Treatment began with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) chemotherapy, followed by radiation therapy to the scalp, both sides of the neck, and left parotid gland. At four-month follow-up, combined positron emission tomography (PET) and CT showed only diffuse low-level uptake in the scalp and parotid gland.

Conclusions: Transformation of low-grade PCFCL to high-grade DLBCL is rare, and the approach to treatment varies. This case showed a good response to chemotherapy and radiation therapy.

MeSH Keywords: Lymphoma, Large B-Cell, Diffuse • Lymphoma, Non-Hodgkin • Lymphoma, Primary Cutaneous Anaplastic Large Cell

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/917389>

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Background

Primary cutaneous follicle center lymphoma (PCFCL), also known as Crosti's lymphoma, is a low-grade B-cell non-Hodgkin lymphoma (NHL) that has an indolent clinical course with a 95% 5-year survival rate [1]. However, transformation of PCFCL to a high-grade B-cell lymphoma, which has a more aggressive clinical course, is associated with a poor prognosis [1]. Although transformation of PCFCL to diffuse large B-cell lymphoma (DLBCL) has previously been reported, the incidence, management, and prognosis have not been well described [1].

A case is reported of a 40-year-old man who presented with a scalp mass that was diagnosed histologically as a PCFCL. Imaging of the head and neck identified DLBCL involving the parotid gland and cervical lymph nodes, which responded well to chemotherapy followed by radiation therapy.

Case Report

A 40-year-old African-American man presented with more than a two-year history of an enlarging scalp mass. He also noticed swelling in his left facial region and lymphadenopathy in his neck during the previous two to three months. He reported one episode of night sweats and weight loss of 20 lbs during the previous month but had no other complaints. His past medical history included diabetes mellitus and hypertension. He had no previous history of malignancy or immunosuppression.

On physical examination, a 10 cm fungating mass was present in the left frontoparietal scalp region (Figure 1A). A separate mass was noted in his left parotid region, and there was bilateral cervical lymphadenopathy. A punch biopsy of the scalp lesion was obtained. The histology showed a low-grade non-Hodgkin lymphoma (NHL) with the formation of indistinct lymphoid follicles. Immunohistochemistry showed that the lymphoma cells were positive for Bcl-6. The histology of the scalp lesion was in keeping with a diagnosis of primary cutaneous follicle center lymphoma (PCFCL) (Figure 1B).

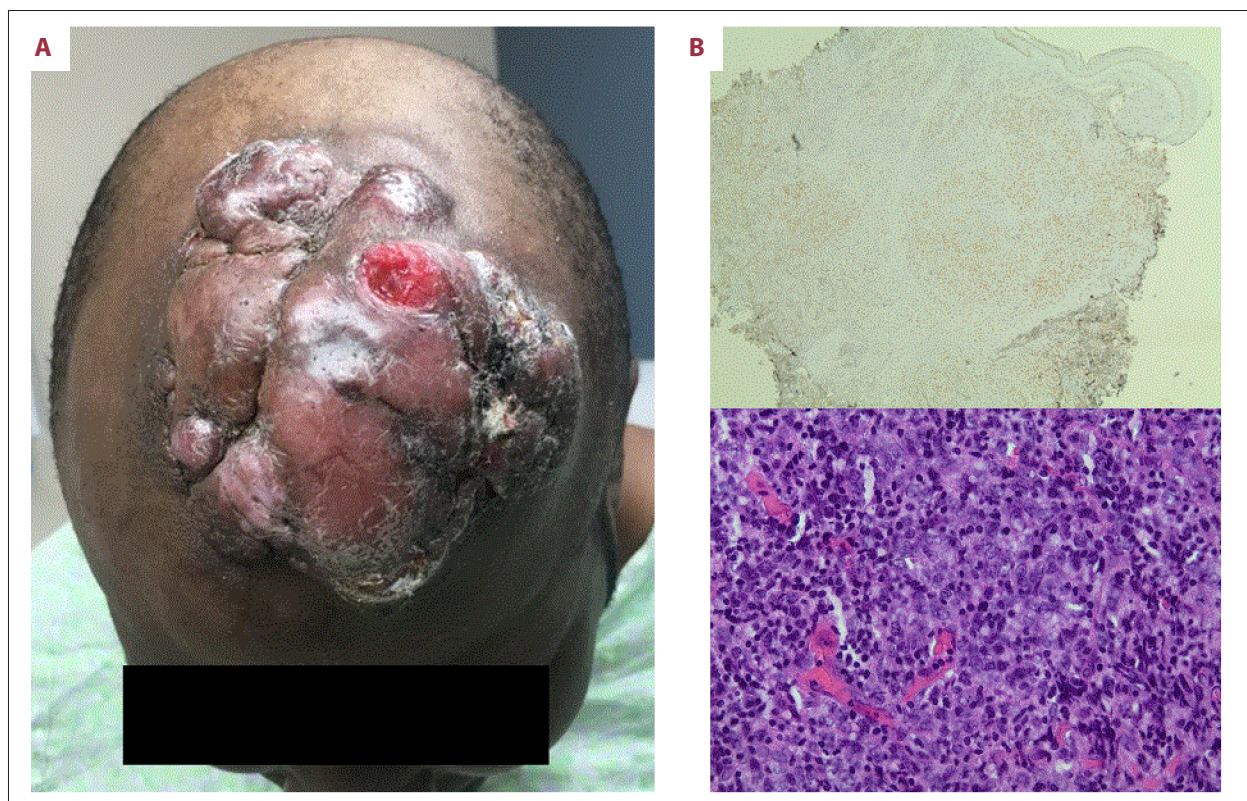


Figure 1. A 40-year-old man with a primary cutaneous follicle center lymphoma (PCFCL) of the scalp with transformation to diffuse large B-cell lymphoma (DLBCL) of the left parotid gland and cervical lymph nodes. (A) A left frontoparietal scalp mass at presentation. (B) (Upper) Photomicrograph of the immunohistochemistry of the biopsy of left frontoparietal scalp mass shows positive immunostaining of the lymphocytes for Bcl-6. (Lower) Photomicrograph of the histology of the biopsy of left frontoparietal scalp mass shows small lymphocytes consistent with a low-grade non-Hodgkin lymphoma (NHL) with a follicular pattern. Hematoxylin and eosin (H&E). Magnification $\times 40$.

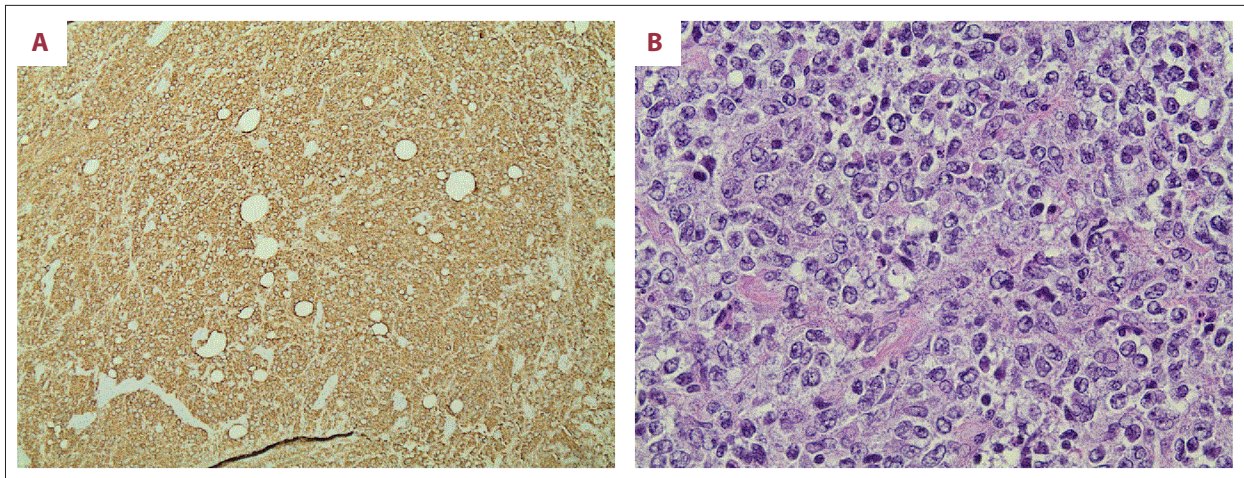


Figure 2. A 40-year-old man with a primary cutaneous follicle center lymphoma (PCFCL) of the scalp with transformation to diffuse large B-cell lymphoma (DLBCL) of the left parotid gland and cervical lymph nodes. (A) Photomicrograph of the immunohistochemistry for CD20 of the biopsy of the parotid gland shows CD20-positive cells. (B) Photomicrograph of the histology of the biopsy of the left parotid gland shows a high-grade non-Hodgkin lymphoma (NHL) consisting of large lymphoid cells with abundant cytoplasm and large oval nuclei, consistent with the appearance of centroblasts. Hematoxylin and eosin (H&E). Magnification $\times 40$.

A computed tomography (CT) scan of the head and neck showed a 10.5 \times 7.1 \times 6.6 cm nodular exophytic mass of the left frontoparietal scalp without erosion into the bone. A 4.9 \times 3.7 \times 3.4 cm mass was found in the left parotid gland, and extensive bilateral cervical lymphadenopathy was present, with the largest lymph node measuring approximately 2 cm.

An excisional biopsy of the parotid mass showed a diffuse large B-cell lymphoma (DLBCL). The cells showed positive immunostaining for CD20 with a high Ki-67 proliferation rate of 80–90% (Figure 2). There was no MYC gene rearrangement, which excluded a diagnosis of a double-hit or triple-hit lymphoma. A positron emission tomography (PET) scan showed hypermetabolic activity of the scalp mass, with a standardized uptake value (SUV) of 14.7, the left parotid gland mass had a SUV of 11.1, and the bilateral cervical lymphadenopathy included a right hilar lymph node with a SUV of 2.8 (Figure 3). Laboratory tests showed an increased serum lactate dehydrogenase (LDH) (287 U/L) and an increased erythrocyte sedimentation rate (ESR) (14 mm/hr). A bone marrow biopsy and lumbar puncture were performed, both of which were negative for lymphoma. Given the long history of the scalp mass and rapid progression of the parotid and neck masses, the patient was clinically diagnosed with stage IIE DLBCL transformed from the stage IE PCFCL of the scalp. However, gene rearrangement studies were not performed to confirm clonality and the transformation in this case.

Treatment commenced with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) chemotherapy. The patient tolerated treatment well, and after the

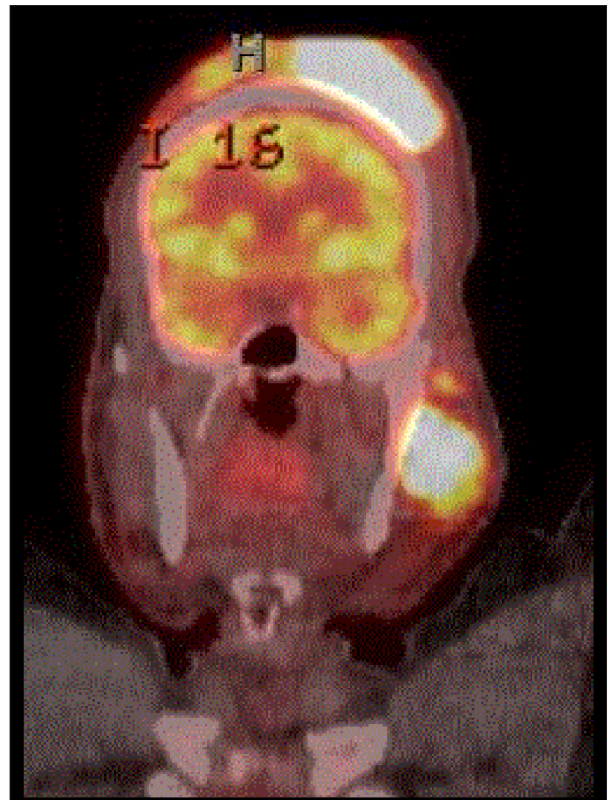


Figure 3. Pre-treatment combined positron emission tomography (PET) and computed tomography (CT) imaging of the head and neck. Pre-treatment combined PET-CT imaging of the head and neck shows a large scalp tumor, a tumor in the left parotid gland, and bilateral involvement of the cervical lymph nodes.

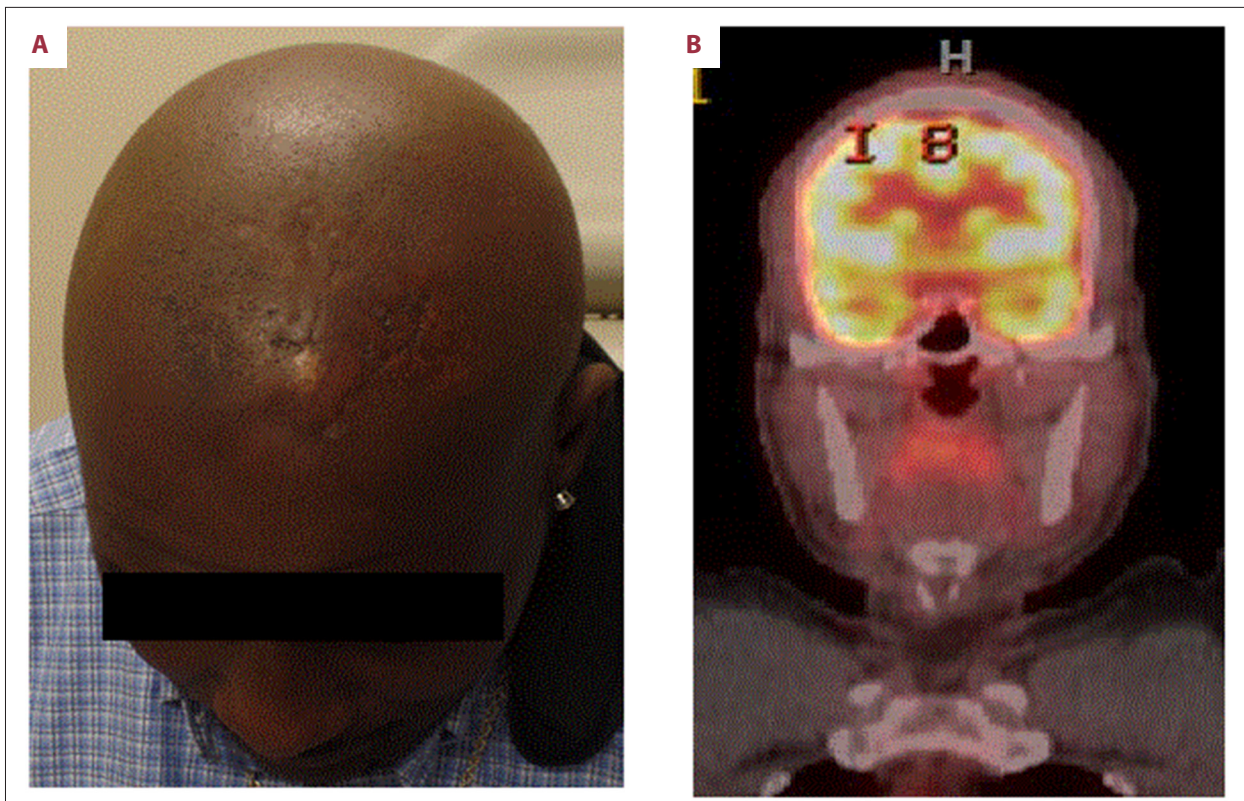


Figure 4. Post-treatment appearance of the scalp at 17 months and combined positron emission tomography (PET) and computed tomography (CT) imaging of the head and neck. (A) The appearance of the left frontoparietal scalp at approximately 17 months following treatment. (B) Post-treatment PET-CT imaging shows resolution of the left parotid mass and the bilateral cervical lymphadenopathy.

sixth cycle of chemotherapy, a PET-CT was obtained to evaluate the response. PET-CT imaging showed a reduction in both the size and SUV of the scalp mass that measured 6×1.5 cm (SUV 1.8) and the left parotid mass that measured 2.5×0.9 cm (SUV 1.4), and there was resolution of the cervical lymphadenopathy. Given the presence of residual disease on PET-CT, the patient continued to receive chemotherapy with a further two cycles of R-EPOCH. Following the completion of eight cycles of chemotherapy PET-CT imaging was repeated, which remained unchanged with the scalp mass measuring 6×1.5 cm (SUV 1.9) and the parotid mass measuring 2.4×0.9 cm (SUV 1.7). The patient also received four doses of prophylactic intrathecal methotrexate. Subsequent analysis of the cerebrospinal fluid (CSF) was negative. The patient was then referred for radiation therapy.

Radiation therapy began with 36 Gy in 18 fractions to the whole scalp, bilateral neck, and left parotid followed by a boost of 9 Gy in five fractions to the residual scalp and parotid lesions. Intensity-modulated radiation therapy (IMRT) with image guidance was used. A custom bolus was applied to the scalp throughout the course of treatment. An 11-field IMRT plan was used for the initial phase, and a five-field IMRT plan was

used for the final phase, both with 6 MV photons. The treatment was given and completed as planned, and radiation to the organs at risk was kept within accepted tolerances. The patient experienced only grade 1 skin toxicity and grade 2 salivary gland toxicity. He responded well to radiation, and at four months post-treatment was without evidence of disease on physical examination. PET-CT imaging at four-month follow-up showed only diffuse low-level uptake in the scalp (SUV 1.8) and parotid gland (SUV 1.5) (Figure 4).

Discussion

Non-Hodgkin lymphoma (NHL) accounts for approximately 4% of all malignancies and has an incidence of 19.5 per 100,000 population [2]. The most common type of NHL is derived from B-cells and accounts for 80–95% of NHL, while the remainder of NHLs are of T-cell or NK cell origin [3]. B-cell NHL is heterogeneous with a wide range of low-grade and high-grade subtypes diagnosed on histopathology. The two most common subtypes of B-cell NHL are follicular lymphoma and diffuse large B-cell lymphoma (DLBCL), which comprise approximately 65% of all cases of NHL [3]. NHL commonly arises from lymphocytes

Table 1. Comparison of this case with previously two previously published case reports of transformation of primary cutaneous follicle center lymphoma (PCFCL) to diffuse large B-cell lymphoma (DLBCL) [8,9].

Author	Patient age (yrs)/gender	Site of PCFCL/DLBCL	Treatment	Outcome
Case Report	40/Male	Scalp/Parotid gland and cervical lymph nodes	R-EPOCH chemotherapy and consolidative radiotherapy	Complete response
Coelho et al., 2010 [8]	44/Male	Back/Stomach	R-CHOP, R-ESHAP, GEMROX, and IFM/VP16 chemotherapy	No response
Perkovic et al., 2017 [9]	60/Male	Chest/Disseminated DLBCL	Surgical resection and R-CHOP chemotherapy	Complete response

PCFCL – primary cutaneous follicle center lymphoma; DLBCL – diffuse large B-cell lymphoma; R-ESHAP – rituximab, etoposide, solumedrone, high-dose cytarabine, and cisplatin; GEMROX – gemcitabine, rituximab, and oxaliplatin; IFM/VP16 – ifosfamide, and etoposide; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

present in the lymph nodes, spleen, and Waldeyer’s ring, but about 25–40% of cases of NHL are extranodal lymphomas [4].

The most common sites of extranodal lymphoma are the gastrointestinal (GI) tract, skin, bone, and brain, but they can arise in almost any tissue [5]. The most common type of primary cutaneous NHL is cutaneous T-cell lymphoma, with the second most common type being primary cutaneous B-cell lymphoma (PCBCL) [6]. PCBCL is a rare malignancy with an estimated annual incidence of 3.1 new cases per 1,000,000 population [6]. PCBCL includes primary marginal zone B-cell lymphoma (PCMZL), primary cutaneous diffuse large B-cell lymphoma (PCDLBCL), and primary cutaneous follicle center lymphoma (PCFCL). PCFCL accounts for approximately 30% of all cases of PCBCL, with an estimated annual incidence of 0.9 new cases per 1,000,000 population [6]. PCFCL usually presents as solitary or group of lesions on the upper body, and the diagnosis is made on histopathology [5].

PCFCL is a slow-growing lymphoma with a good prognosis, depending on the location, but has a high rate of local recurrence [5]. PCFCL of the head and scalp has an estimated 5-year survival of 95% [5]. Treatment is by radiation therapy, but surgery or even clinical observation are treatment options for small foci of PCFCL [5]. However, a recognized risk associated with PCFCL is transformation or progression to a more aggressive form [5]. The rate of transformation of PCFCL is unknown, but follicular lymphoma has been reported to have a 3% annual risk of transformation [7]. A review of the published literature has identified two previously reported cases of transformation of PCFCL to DLBCL (Table 1) [8,9].

One of the two previously reported cases was of a 44-year-old Caucasian man with a ten-year history of slowly enlarging skin lesions on his back that were initially biopsied and diagnosed as an inflammatory pseudolymphomatous reaction, treated with tetracycline that resolved after sun exposure [8].

Three years later, he presented with epigastric pain and weight loss and was diagnosed with gastric DLBCL from a gastric biopsy [8]. Review of the histopathology from his prior back lesions showed a low-grade B-cell NHL that was weakly positive for Bcl-2, negative for CD10, and positive for CD20 and Bcl-6, which resulted in a change in diagnosis to PCFCL [8]. An identical clonal VH–JH gene rearrangement was identified in both the PCFCL and the DLBCL cells that confirmed transformation [8]. The patient received chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), but with no improvement [8]. An additional three lines of chemotherapy were given that included rituximab, etoposide, solumedrone, high-dose cytarabine, and cisplatin (R-ESHAP), gemcitabine, rituximab, and oxaliplatin (GEMROX), and ifosfamide and etoposide (IFM/VP16), but with no response (Table 1) [8].

The second of the two previously reported cases was of a 60-year-old man who was initially diagnosed with a PCBCL lesion on his chest [9]. The patient underwent surgery to remove the lesion and experienced a local recurrence two years later [9]. The recurrence was noted to be slow-growing, and he was managed conservatively by clinical observation [9]. After ten years of observation, the lesion began to grow rapidly and disseminate [9]. A biopsy showed primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) [9]. The patient was treated with R-CHOP, which resulted in a complete response, and he was reported to be disease-free for three-years at the time of this report (Table 1) [9].

Studies on follicular lymphoma support that clonal transformation of PCFCL to DLBCL is associated with poor prognosis [7]. The 5-year survival following the transformation of follicular lymphoma into DLBCL ranges from an estimated 10–66%, based on the extent of disease, with limited disease having a better prognosis [7]. However, there has been improved survival of patients with transformed DLBCL following the use of rituximab, with some studies showing a 5-year survival ranging

from 46–72%. Furthermore, the recently reported National LymphoCare Study, which looked at the incidence, prognostic features, and outcomes associated with transformation in 2,642 patients with follicular lymphoma found that patients presenting with transformation at diagnosis had 5-year progression-free survival (PFS), and an overall survival (OS) of 66% and 88%, respectively, which is similar to patients without transformation [10]. Treatment for patients with transformed PCFCL into DLBCL follows that for DLBCL, with chemotherapy using R-CHOP or R-EPOCH, and adjuvant therapy as indicated [11]. R-EPOCH may be a better treatment in patients with high Ki-67 expression, which is a marker of cell proliferation, and low-intermediate International Prognostic Index (IPI) [12]. As this case has shown, transformed lymphoma is a challenging disease to treat as there are yet no clear management guidelines.

Conclusions

As this case report has shown, that primary cutaneous follicle center lymphoma (PCFCL), a low-grade B-cell non-Hodgkin lymphoma (NHL), can be an indolent disease. PCFCL usually has an excellent prognosis with an average 5-year survival of 95%. However, the transformation of PCFCL into a more aggressive form has an uncertain prognosis, and there are no guidelines on clinical management. Because the transformation of follicular lymphoma to diffuse large B-cell lymphoma (DLBCL) has associated with a poor outcome, but recent developments in chemotherapy have improved the outcome. However, clinical studies on the prognosis of transformed PCFCL and treatment outcomes are awaited. Two previously reported cases of transformation of PCFCL to DLBCL showed different outcomes following chemotherapy, which supports the need for further studies to determine the optimal treatment in cases of PCFCL transformation. It remains to be seen what the long-term outcome will be for the patient described in this report.

Conflict of interest

None.

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