Case Study

Epstein-Barr virus-associated transformation of primary cutaneous follicle center lymphoma to diffuse large B-cell lymphoma, a case and review of the literature

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Abstract: Primary cutaneous follicle center lymphoma (PCFCL) is a rare, indolent neoplasm with a good prognosis. Transformations of PCFCL into more aggressive non-Hodgkin lymphomas, such as diffuse large B-cell lymphoma (DLBCL), are extremely uncommon, with few cases reported in the literature. We present a case report of an 84-year-old man with a history of PCFCL who presented 26 months after initial treatment with an enlarged lymph node in the right neck. Excisional biopsy revealed DLBCL. Further studies showed the presence of Epstein-Barr virus (EBV), and molecular studies were consistent with the two neoplasms being clonally related. Taken together, these findings suggest an EBV-driven transformation of PCFCL to DLBCL in this patient.

Keywords: Primary cutaneous follicle center lymphoma (PCFCL); Epstein-Barr virus (EBV); diffuse large B-cell lymphoma (DLBCL); transformation

Introduction

Primary cutaneous follicle center lymphoma (PCFCL) is the most common primary B-cell tumor of the skin, and accounts for over half of the primary cutaneous B-cell lymphomas [1]. It often occurs on the head, neck, or trunk, and most commonly affects middle-aged to older adults. Lesions are composed of centrocytes and centroblasts, with varying architectural patterns of growth [2]. The cause of PCFCL is unknown, but viral and bacterial etiologies have been postulated [1]. PCFCL is extremely responsive to radiotherapy, and dissemination beyond the skin is rare even without treatment [3]. Lesions frequently recur after treatment, but this has little impact on outcome with an estimated 5-year survival rate of 95-97% [1, 2]. Transformation of PCFCL to high-grade diffuse large B-cell lymphoma (DLBCL) is rare, with few reports in the literature [4–7].

Epstein-Barr virus (EBV) is a well-studied oncogenic virus that contributes to the formation of many B-cell lymphomas, and has been associated with the transformation of indolent lymphomas to more aggressive forms [8]. Here we report a case of EBV-positive DLBCL that appears to have arisen from a low-grade precursor PCFCL.

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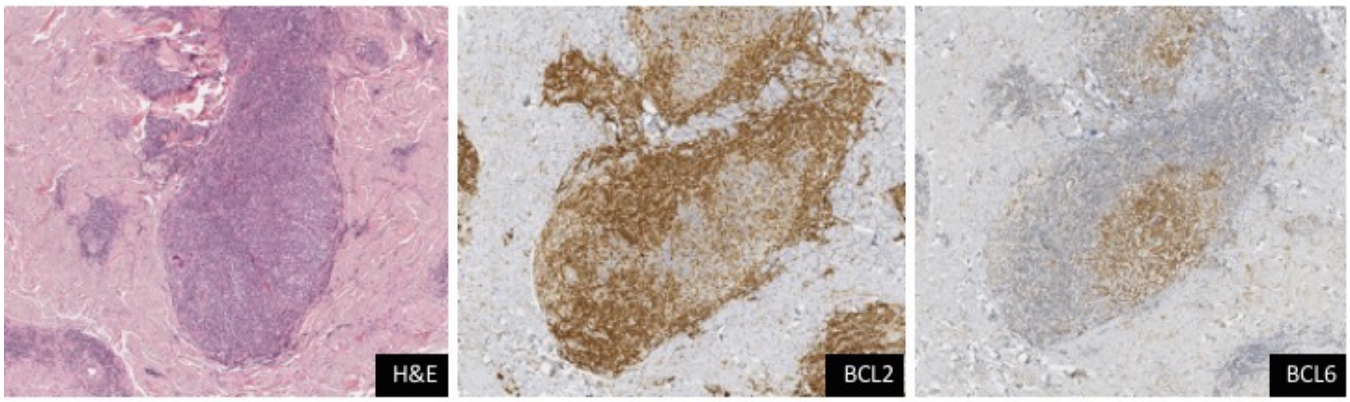

Figure 1: Cutaneous biopsy from skin of patient's right neck. H&E stain shows a dense, follicular growth pattern of atypical lymphocytes within the dermis, which are positive for BCL6 and negative for BCL2.

Case Report and Pathologic Findings

An 84-year-old man with an unremarkable medical history presented with a cutaneous lesion on his right neck. Biopsy showed a nodular infiltrate of atypical lymphoid cells inhabiting the full thickness of the dermis (Figure 1). Immunohistochemical stains showed the atypical cells were positive for CD20, BCL6, and PAX5. MUM1 highlighted a few scattered B-cells. Stains for CD10 and BCL2 were negative. Staining for CD43 was interpreted as only showing positivity among T-cells. CD21 and CD23 highlighted follicular meshworks associated with the nodules. The Ki-67 proliferation index was approximately 60%. Based on these findings the case was diagnosed as a PCFCL versus cutaneous involvement by systemic follicular lymphoma (FL). Computed tomography (CT) scans of the chest, abdomen, and pelvis revealed no suspicious mass lesions, thus supporting a diagnosis of PCFCL.

A follow-up positron emission tomography (PET) scan at 6 weeks was negative, and at 23 weeks showed increased avidity in the midline thyroid. This site was biopsied and found to be reactive lymphoid hyperplasia of the thyroid isthmus. A PET scan performed at 15 months revealed increased avidity within the proximal shaft of the right femur, with a standardized uptake value (SUV) of 10.7. This was considered to be a probable isolated recurrence of the B-cell lymphoma, and the patient underwent local radiation therapy with apparent resolution of the lesion. No biopsy was performed.

At 23 months after initial diagnosis the patient presented with a mass lesion at the base of the tongue, and bilateral biopsies were obtained in addition to sampling of the inferior tonsils. These were initially interpreted as benign reactive lymphoid hyperplasia, but later reexamination showed foci of subtle lymphoma involvement, highlighted by aberrant B-cell expression of CD43.

At 26 months the patient presented with a mass lesion in the right neck and underwent excisional biopsy of an enlarged lymph node. Microscopic examination showed effaced architecture with a diffuse proliferation of intermediate to large lymphoid cells with patchy necrosis (Figure 2). Immunohistochemical staining revealed the neoplastic cells were positive for CD20, CD30 (variable), CD43 (dim), and MUM1. EBV latent membrane protein 1 (LMP1) was positive in a subset of cells, most conspicuous in areas that also showed CD30 expression. The cells were negative for CD3, CD5, CD10, cyclin D1, BCL2, and BCL6. Expression of Ki-67 was variable but observed to be >90% in the most active regions. In situ hybridization for EBV-encoded small RNAs was positive. A diagnosis of DLBCL was made.

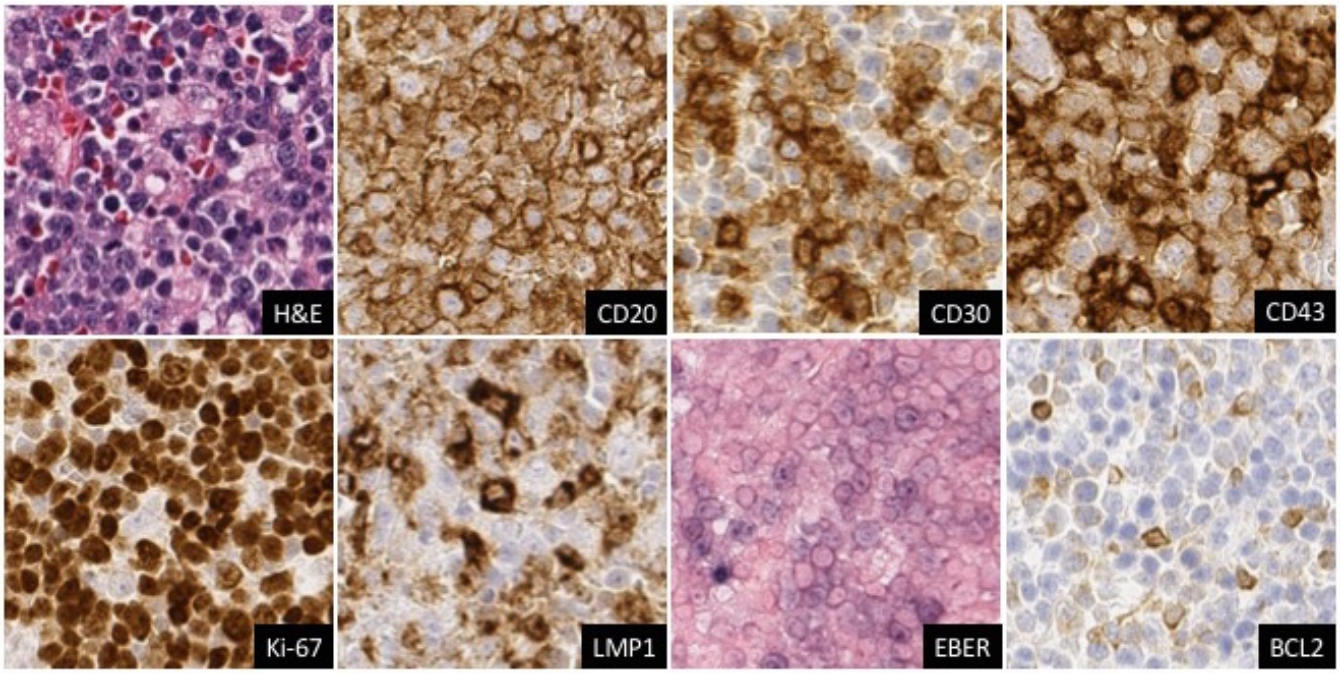

Figure 2: Excisional lymph node biopsy from patient's right neck. High power view showing intermediate to large lymphoid cells with frequent mitoses. Immunohistochemical stains showed the cells were positive for CD20, CD30 (variable), CD43 (dim), and LMP1. The Ki-67 proliferation index was very high (>90%) in some regions. In situ hybridization for EBV-encoded small RNAs (EBER) was focally positive. The atypical cells were negative for BCL2.

Eight-color flow cytometric analysis of the lymph node specimen detected a dominant population of atypical lymphocytes (57% of gated events) that were positive for CD19, CD20, CD30 (subset), CD38, CD43 (partial), CD45, and HLA-DR. They were negative for CD3, CD5, CD10, CD23, CD56, CD57, FMC-7, surface kappa, surface lambda, cytoplasmic kappa, and cytoplasmic lambda.

Polymerase chain reaction (PCR) analysis of the *IGH* gene detected a clonal rearrangement of the Framework 3 (FR-III) region, with a dominant band at approximately 50 bp (Figure 3). Karyotyping showed an abnormal male karyotype, with duplication of a segment of the long arm of chromosome 1 (q12q32) in 12 of 20 analyzed metaphase cells. The remaining 8 cells had a normal male karyotype. Retrospective PCR analysis of the cutaneous lesion detected a dominant band of approximately 50 bp amplified from the *IGH* gene's FR-III region, similar to that described above.

Details of the patient's follow-up and subsequent oncologic treatment are not known to the authors.

Summary of Previous Cases

Case 1 [4] - A 44-year-old male presented with pruritic, erythematous cutaneous nodules on the back that gradually coalesced into a single lesion over 10 years. A biopsy was interpreted as an inflammatory pseudolymphomatous reaction. Three years later he was diagnosed with gastric DLBCL occurring in a background of *Helicobacter pylori*-positive gastric ulcers. Imaging studies showed enlargement of the mediastinal and axillary lymph nodes. Reexamination of the cutaneous biopsy resulted in reclassification of the skin lesion as PCFCL. PCR analysis of the *IGH* gene in both specimens revealed amplification products of identical sizes, which supported

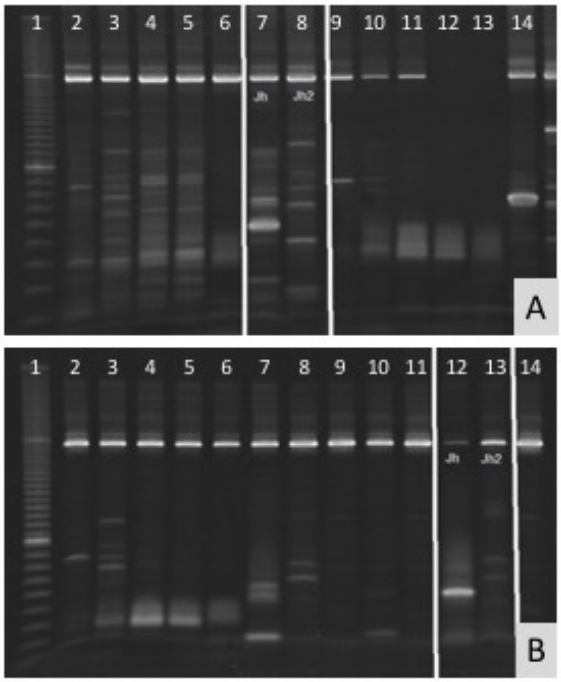

Figure 3: Agarose gels showing PCR amplification products from the FR-III region of the *IGH* gene (patient's samples are noted by Jh and Jh2). 3A, Amplification from the cutaneous biopsy specimen diagnosed as PCFCL. *Lane 1*: DNA ladder with bright band at 100 bp and smaller bands in 10 bp increments. *Lanes 2-6*: Unrelated samples. *Lane 7 (Jh)*: A dominant band at approximately 50 bp. *Lane 8 (Jh2)*: Multiple bands of varying intensity. *Lanes 9-14*: Unrelated samples. 3B, Amplification from the excisional lymph node biopsy diagnosed as DLBCL. *Lane 1*: DNA ladder with bright band at 100 bp and smaller bands in 10 bp increments. *Lanes 2-11*: Unrelated samples. *Lane 12 (Jh)*: A dominant band at approximately 50 bp. *Lane 13 (Jh2)*: Two bands at approximately 60 and 75 bp, respectively, have possible counterparts in the corresponding lane in 3A. *Lane 14*: Unrelated sample.

clonality. The patient was treated with four separate chemotherapy regimens without response.

Case 2 [5] - A 50-year-old man presented with a nodular erythematous lesion on the forehead and scalp that progressed over 2-3 years. His history was significant for a testicular teratoma 13 years prior that was treated successfully with a combination of surgery and chemotherapy. The cutaneous lesion was biopsied and diagnosed as PCFCL, and the patient was subsequently treated with radiotherapy, which resulted in a partial response. At 32 months after initial diagnosis, and 29 months after completing radiotherapy, the patient developed an enlarged right submandibular lymph node. Excision showed DLBCL which was positive for EBV by both in situ hybridization (EBER) and immunostaining for LMP1. Immunostaining for EBNA2 was negative. Retrospective analysis of the skin lesions revealed they were similarly positive for EBV. The patient was treated with R-CHOP, went into remission, and underwent autologous peripheral stem cell transplant. He subsequently developed a therapy-related myeloid neoplasm.

Case 3 [6] - A 60-year-old man presented with a diagnosis of primary cutaneous DLBCL-other (PC-DLBCL-O) on his chest. The process had first appeared 13 years prior as a solitary erythematous lesion on the chest. It was excised and diagnosed as PCFCL. Two years later the lesion recurred, and during the subsequent interval it slowly grew and spread to nearby cutaneous sites on the trunk. A new biopsy of the primary lesion was performed,

which showed a lymphoid tumor with morphologic and immunohistochemical features of DLBCL. The patient was treated with R-CHOP and went into complete remission.

Case 4 [7] - A 40-year-old man presented with a scalp mass of 2-years duration, and 2-3 months of unilateral facial swelling and bilateral cervical lymphadenopathy. Biopsy of the scalp mass showed a low-grade cutaneous lymphoproliferative lesion that was interpreted as PCFCL. A CT scan showed a mass in the parotid gland and multiple enlarged lymph nodes, one of which was excised. Histologic examination showed DLBCL, and molecular analysis did not reveal a rearrangement of MYC. The patient was treated with R-EPOCH, intrathecal methotrexate, and radiotherapy with good response.

Discussion

This case report adds to existing literature that transformation of PCFCL to a high-grade lymphoma is rare but does occur. Several lines of evidence support that this patient's PCFCL was the direct precursor of his later diagnosed DLBCL. These include the close anatomic and temporal association of the two lesions, PCR amplification products of similar sizes, and the absence of immunoglobulin expression (which would be unusual for a de novo DLBCL but is commonly observed in PCFCL) [2]. The presence of a known oncogenic virus also provides a plausible mechanism for transformation.

Evidence that supports non-relatedness of the two neoplasms largely rests on differences in immunophenotype, with apparent loss of Bcl-6 and gain of dim CD43 expression in the DLBCL. The significance of this variation is unclear, but may reflect underlying genetic changes associated with transformation.

With regard to CD43, this marker is positive in approximately 25 percent of DLBCLs and it has been found to be an independent negative prognostic factor for overall survival [9]. The expression of CD43 in PCFCL is unusual. Of the cutaneous B-cell lymphomas, its presence would be more typical of primary cutaneous marginal zone lymphoma [10]. A lack of CD43 expression was noted in the original cutaneous biopsy. This may represent gain of an aberrant surface marker, although expression of dim CD43 in the neoplastic cells would be difficult to discern amongst a background of normal T- and B-cells.

Compared to the other reports of PCFCL transformation, the patient in this case was considerably older (84 years versus a mean of 48.5 years). Advanced age is a recognized risk factor for the development of a variety of EBV-related lymphoproliferative disorders, presumably due to age-related senescence of T-cell immunity [11]. Three of the four previous cases did not report testing for EBV, so its potential role in pathogenesis of those neoplasms is unclear.

In summary, we present a case of PCFCL that likely transformed to an EBV-associated DLBCL. Further research is warranted to discern the general prevalence of EBV in cases of PCFCL, and to better characterize the expression of CD43 in these lesions.

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