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Bilateral auricular lymphoplasmacytic lymphoma: barely mere coincidence.☆,☆☆

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ABSTRACT

We describe the first case of LPL simultaneously involving both auricles. Affected ears were the first manifestation of the disease that led to the diagnosis. The lack of appreciable systemic disease allowed sparing the patient from immunochemotherapy. Radiation therapy was used as a single modality and secured a stable remission. A putative pathogenesis of the paired auricular lymphoma is discussed and a literature review presented. While the role of genetic predisposition in our patient was uncertain, we postulate that symmetric ear lymphoma could have been caused by a combined effect of the homing of malignant lymphocytes whose localized growth was triggered by the hazardous environmental exposure.

1. Introduction

Simultaneous presentation of non-Hodgkin lymphoma in paired organs is rare and visually striking. While symmetrical lymphomas involving breasts, kidneys, adrenals have been infrequently reported, bilateral ear involvement is unique. We present the first reported case of lymphoplasmacytic lymphoma concomitantly affecting both auricles. The patient was treated with radiotherapy to both ear lesions with an excellent response. A putative pathogenesis of the paired auricular lymphoma is discussed and a literature review presented.

2. Case report

A 63-year-old generally healthy man presented with an 8-month history of enlarging and tender skin lesions involving the helices of both ears. The patient denied fever, night sweats, weight loss or symptoms of neuropathy. There was no history of hepatitis C or autoimmune disorders. He had no personal or family history of malignancies or illnesses associated with immunodeficiency. The patient worked in car production and reported exposure to oil-containing metalworking fluids for 25 years. The patient's physical examination was unremarkable with no palpable lymph nodes or hepatosplenomegaly. Both ears displayed irregular, slightly tender soft tissue infiltrates (Fig. 1A/B). On biopsy, the skin of the left superior ear lesion showed dense, dermal lymphoplasmacytic infiltrate (Fig. 2A) composed of abundant kappa restricted plasma cells (Fig. 2B/C) expressing CD138 and CD20 (Fig. 2D). The sections showed the cells positive for BCL-2, BCL-6, Mum1, Pax5 and c-MYC, while negative for CD5, CD10, CD43, BCL 1, SOX-11, CD30 or EBER. Proliferation rate measured by Ki67 was 30%. No amyloidosis was identified, and stain for *Treponema pallidum* showed no organisms. The findings supported a cutaneous (extranodal), kappa-restricted lymphoplasmacytic lymphoma (LPL). The patient's CBC counts and differential were normal, LDH 144 U/L (reference range, <=270 U/L). HIV and a hepatitis panel were negative. Serum protein electrophoresis revealed monoclonal protein (1.2 g/dL) in beta region that was identified by immunofixation as IgM, kappa type. MYD88 L265P mutation was identified in peripheral blood by a PCR-based pyrosequencing method. A positron emission tomography/computed tomography (PET/CT) scan showed scattered, nonspecific, borderline to minimally enlarged and very mildly FDG-avid nodes above the diaphragm most notably in bilateral axillae but without FDG-avid splenic or bone marrow lesions. The patient was diagnosed with an extranodal (cutaneous) LPL. The patient received external beam radiation to both earlobes to a total dose of 3000 cGy in 15 fractions with complete resolution of the lesions (Fig. 1, C/D). Follow up PET/CT scans demonstrated very mild, waxing and waning lymphadenopathy. Currently, the patient feels well without

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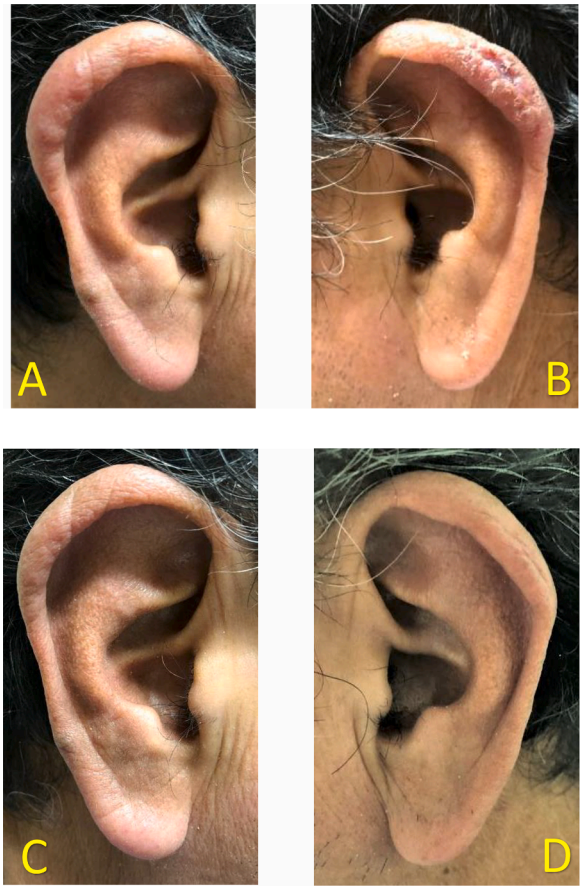

Fig. 1. A and B: Bilateral auricular lesions. Left ear after the biopsy. C and D: Both ears after radiation therapy.

any symptoms of relapse with a slightly increased serum IgM paraprotein (1.5 g/dL) 20 months after completing radiation therapy treatment.

3. Discussion

Concurrent bilateral auricular involvement with lymphoma is exceedingly rare. To date, only five cases were reported including centrocytic/centroblastic (CC/CB) lymphoma [1], marginal zone lymphoma (MZL) [2] and three cases of small lymphocytic lymphoma (SLL) (Table 1) [1,3,4]. Additionally, twelve cases have been reported in chronic lymphocytic leukemia (CLL) (Table 1) [5]. To our knowledge, simultaneous LPL affecting both ears has not been described. Because of the extreme rarity of bilateral auricular lymphomas, any possible and perhaps unique pathogenetic circumstances ought to be considered.

3.1. Infection and inflammation

Because B cells, unlike T cells, are virtually undetectable in the normal skin, their migration to the skin (and other extra-lymphatic sites) presumably occurs almost exclusively in the context of chronic inflammation driven by locally persistent antigen [6]. *Borrelia burgdorferi* and herpes virus (mostly zoster, rarely simplex) in the skin, *Helicobacter pylori* in the stomach, *Chlamydia psittaci* in ocular adnexa, and autoantigens in Sjogren disease are the examples of lymphoma triggers acting via chronic antigenic stimulation. Goudie et al[1] suggested that bilateral auricular lymphomas may develop as a result of malignization of pre-existing benign inflammatory or autoimmune skin disorders that can present with *bilateral* distribution such as vitiligo, psoriasis and pityriasis lichenoides et varioliformis acuta (PLEVA). Another example

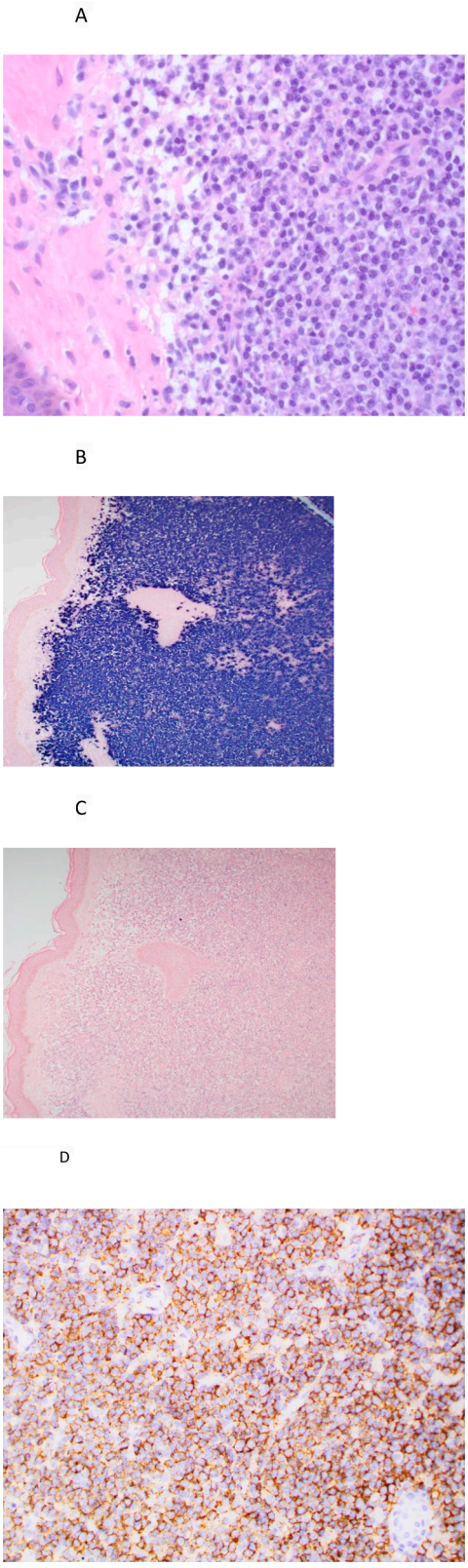

Fig. 2. Left ear skin biopsy. A section demonstrates dense dermal infiltrate composed of mature appearing lymphocytes and abundant plasma cells, 40x (A) that show kappa light chain stain, 10x (B), lack of lambda light chain stain, 10x (C), and CD20 expression, 20x (D).

Table 1
Some clinical data on the patients with CLL and lymphoma with bilateral auricular involvement including the present case.

Cases	Age, years	Sex	Clinical lesions	Symptom duration	Treatment	Outcome	Systemic disease
CLL[5]: Early ($n = 7$)	39–73	M	Mostly erythematous nodules	2, 4 and 5 years in three patients, unknown in four	UVB[a] EBT[b], RT[c], R-CVP[d]chlorambucil+obinutuzumab,	Six regressed, one unknown	Present by definition
Late ($n = 5$)	57–67	M	Plum-colored or erythematous swelling, papules or lesions	4 months and 8 years; unknown in three	None in one, RT in two, FCR[e], unknown in one	Regressed in three; aggravated in one, not known in one	Present by definition
Lymphomas: SLL[3] SLL[4] SLL[1]	56	M	Irregular skin with solitary, firm swellings in both ear lobules	12 months	Bilateral excisions, chemotherapy for 1st relapse, XRT for 2nd relapse	Disease-free 96 months after presentation	None[f]
CC/CB[1] MZL[2]	45	M	Bilateral nodular lesions	2 years	XRT (two sessions), steroids and XRT a relapse on nasal tip	unknown	Subtle[g]
LPL (current case)	57	M	Enlargement and induration of both earlobes	6 months	XRT only, Chlorambucil for systemic relapse 7 years after dx; NED 13 years after the dx	Progressed 5 years later: lymphocytosis, splenomegaly	Present (enlarged lymph nodes)
	54	M	Swelling and pain, worse in cold. Helices and lobes with irregular nodular swelling	3 years	CVP x 6	In remission one year after treatment	Subtle[h]
	66	M	Swelling plaques	2 months	Chemotherapy (R-CHOP)	unknown	Present (lymphocytosis and enlarged lymph nodes)
	63	M	Small nodules in helices	8 months	Bilateral XRT	Symptom-free 20 months after presentation	Subtle[i]

[a]UVB: ultraviolet light B.
[b]EBT: electron beam therapy.
[c]RT: radiation treatment.
[d]R-CVP: rituximab, cyclophosphamide, vincristine, prednisone.
[e]FCR: fludarabine, cyclophosphamide and rituximab.
[f]flow cytometry not performed and no CT documented.
[g]blood flow cytometry suggested monoclonal lymphocytosis.
[h]lymphoid aggregates in two bone marrow specimens.
[i]blood flow cytometry showed monoclonal lymphocytosis.

is relapsing polychondritis (RP) that, at the time of presentation, may cause bilateral inflammation of the ears. Similar mechanism has been suggested in cases of a so-called Koebner-like phenomenon (isomorphic response) describing a skin disease that develops at the site of skin irritation or trauma like a cut, a bruise or a burn. A peculiar example is pseudolymphoma due to pierced earlobes [7]. Our patient had no apparent history of pre-existing ear inflammation other than the tender skin lesions predating the diagnosis by eight months. Additionally, *T. pallidum* stain that identifies *Borrelia burgdorferi* as well failed to detect spirochetes. In cases of prolonged auricular swelling and pain, a possibility of pre-existing premalignant inflammation should be considered.

3.2. Homing

The aforementioned authors [1] hypothesized that preferential "homing" (accumulation) and/or growth of circulating tumor cells at specific anatomical sites may occur because of interaction of clonal lymphocytes with site-specific ligands. This process replicates in part a complex process of normal lymphocyte homing and is similarly regulated by adhesion molecules (selectins and integrins) and chemokines [8]. Lymphocyte subsets and endothelial cells (auricular skin is well furnished with vascular plexuses) specifically program their expression of adhesion molecules, chemokines/chemokine receptors (CCR7 and CXCR4), and major chemo attractants for B cells CXCL12 and CXCL13 allowing lymphocytes to move to specific functional compartments of the immune system, such as the mucosa-associated lymphoid tissue and the skin [6]. The "homing hypothesis" has to assume the presence of systemic lymphoma in the background as a source of the cell subsets with specific homing properties. So far, the systemic disease has been established in all but one reported case. Our patient too, despite the lack of convincingly identifiable lymphoid organ involvement, demonstrated, in addition to a circulating monoclonal serum IgM, a small kappa-restricted B cell population in the peripheral blood (positive for CD19, CD20, dim partial CD5, CD23, FMC7, CD200, dim partial CD123, and negative for CD10, CD38, CD11c or CD103). A proliferation rate Ki67 up to 30% on the biopsy was consistent with a proliferative process rather than a mere accumulation of abnormal lymphocytes.

3.3. Genetics

Some tumors developing in paired organs are assumed genetically determined because of an associated family history and an earlier age at onset. While a genetic model has not been previously applied to bilateral lymphomas, of interest is the observation that about 20% of patients with LPL have been reported to have a positive family history of hematologic malignancy in first-degree relatives [9] as well as earlier age at presentation. Interestingly, four of seven CLL patients who presented with bilateral ear lymphomas were only from 39 to 45 years old [5] and all lymphoma patients were approximately 10 years younger than the average age at diagnosis for their corresponding lymphoma type (Table 1) [9]. By comparison, bilateral tumors such as retinoblastoma and Wilms' tumor are believed to be hereditary that develop according to a "two-hit" model that implies two gene mutations in a tumor-suppressor gene [10]. It would be probably exaggeration to assume that, during embryogenesis, both ears could develop from a single clonal event as it has been shown for clonal nephrogenesis in Wilms's

tumor [11]. It is noteworthy, however, that deletion of 17p13.3–p12 containing a tumor-suppressor gene *TP53* was identified in 15% of lymphoplasmacytic lymphomas [12]. From the genetic perspective, another intriguing observation is that all the cases of bilateral auricular involvement by lymphoma and CLL (n = 18) occurred in males (Table 1).

3.4. Environment

The simultaneous development of lymphoma in both pinnae prompts consideration of environmental factors. Our patient was working in car production associated with extended exposure to potentially hazardous vapors and sprays from the oil-containing metalworking fluids without consistent use of protective gear. Such exposure can potentially induce inflammation leading to persistent antigenic stimulation with resultant neoformation of lymphoid tissue [6]. In this regard, it is important to point out that, for example, ocular adnexa is associated with bilateral lymphomas more commonly than could be explained by mere coincidence. Thus, 43% of patients with mantle cell lymphoma affecting conjunctiva and eyelid presented with bilateral involvement [13]. Likewise, bilateral lesions are common in patients with orbital CLL/SLL (50%) and LPL (60%). Such seemingly non-random bilateral lymphomas affecting ocular adnexa suggest a plausible effect of adverse environmental factors. It is reasonable to speculate that the cumulative effect of environmental factors during the individuals' lifespan could disproportionately affect the head region because unprotected skin and mucous membranes of the head could be at more risk of a direct and repetitive exposure by external toxins and irritants compared to other (protected) parts of the body. Similar mechanism could also explain more common occurrence of *leukemia cutis* in the head and neck areas in CLL patients. The environmental concept would not contradict the "two-hit theory" in our patient, but unlike in inherited tumors, the second hit would not initiate a tumor, but would rather alter the tumor B cells into a subset with unique homing properties and more aggressive proliferative features (as shown in cutaneous CLL cases). Such mechanism would imply pre-existing malignant lymphocytes either residing in affected areas or their migration to the areas of irritated or inflamed skin.

Limited literature data [3] and our own observation suggest that, in the absence of symptomatic systemic lymphoma, XRT is a preferred treatment option for auricular lymphoma that may delay or obviate the need for systemic treatment. None of the patients with bilateral ear involvement demonstrated adverse prognosis.

4. Conclusion

We describe the first case of LPL simultaneously involving both auricles. Affected ears were the first manifestation of the disease that led to the diagnosis. The lack of appreciable systemic disease allowed sparing the patient from immunochemotherapy. Radiation therapy was used as a single modality and secured a stable remission. While the role of genetic predisposition in our patient remains uncertain, we postulate that symmetric ear lymphoma could have been caused by a combined effect of the homing of malignant lymphocytes whose localized growth was triggered by the hazardous environmental exposure. Future deliberate observational studies attentive to clinical details could shed more light on the intriguing nature of bilateral lymphomas.

Declaration of Competing Interest

The authors have no conflict of interests.

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