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...
any symptoms of relapse with a slightly increased serum IgM para-
protein (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 cen-
trocytic/centroblastic (CC/CB) lymphoma [1], marginal zone lymph-
oma (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 inflam-
mation 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 auto-
antigens in Sjogren disease are the examples of lymphoma triggers
acting via chronic antigenic stimulation. Goudie et al. 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. 1. A and B: Bilateral auricular lesions. Left ear after the biopsy. C and D:
Both ears after radiation therapy.

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

| Cases          | Age, years | Sex | Clinical lesions | Symptom duration | Treatment                                                                 | Outcome                                                                 | Systemic disease                        |
|---------------|------------|-----|------------------|------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------|
| CLL§; Early (n = 7) | 39-73      | M   | Mostly erythematous nodules | 2, 4 and 5 years in three patients, unknown in four | UVB§ EBT§, RT§, R-CVP§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§, unknown in one | Regressed in three; aggravated in one, not known in one | Present by definition |
| Lymphomas:     |            |     |                   |                  |                                                                           |                                                                         |                                       |
| SLL§          | 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§ |                                       |
| SLL§          |            |     |                   |                  |                                                                           |                                                                         |                                       |
| SLL§          |            |     |                   |                  |                                                                           |                                                                         |                                       |
| CC/CL3        | 45         | M   | Bilateral nodular lesions | 2 years          | XRT (two sessions), steroids and XRT a relapse on nasal tip | unknown                  | Subtle§ |                                       |
| MZL3          | 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) |                                       |
| LPL (current case) | 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§ |                                       |
| LPL (current case) | 66 | M | Swelling plaques | 2 months        | Chemotherapy (R-CHOP) | unknown                  | Present (lymphocytosis and enlarged lymph nodes) |                                       |
| LPL (current case) | 63 | M | Small nodules in helices | 8 months         | Bilateral XRT | Symptom-free 20 months after presentation | Subtle§ |                                       |

§UVB: ultraviolet light B.
§EBT: electron beam therapy.
§RT: radiation treatment.
§R-CVP: rituximab, cyclophosphamide, vincristine, prednisone.
§FCR: fludarabine, cyclophosphamide and rituximab.
§flow cytometry not performed and no CT documented.
§blood flow cytometry suggested monoclonal lymphocytosis.
§lymphoid aggregates in two bone marrow specimens.
§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 with bilateral ear lymphomas 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.

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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 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].

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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 immunotherapy. 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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