Simultaneous intraocular and cutaneous extranodal NK/T cell lymphoma refractory to multiple therapies including pembrolizumab

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Abstract

An 80 year old woman underwent vitrectomy for recurrent uveitis, demonstrating lymphocytic vitreous fluid. Less than a month later skin biopsy confirmed the diagnosis of extranodal NK/T cell lymphoma. Chemotherapy with SMILE (steroid - dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) was poorly tolerated despite reduced doses, while pembrolizumab was ineffective.

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Key Clinical Message: Floaters or visual disturbance in a patient with ENKL should prompt evaluation for possible vitreoretinal involvement. Lymphoma with ocular involvement should be treated aggressively and in most cases heralds CNS involvement.

Introduction

Extranodal NK/T cell nasal type lymphoma (ENKL) is an aggressive malignancy which presents with a midline destructive lesion in the upper respiratory tract in 60 to 90% of patients. [1-4] ENKL is most common in Asian and Hispanic populations where it accounts for approximately 5% of lymphoma, however it is rare in Western populations.[5,6] The characteristic features of the disease are expression of NK cell markers (CD2, CD3, CD56), cytotoxic molecules (granzyme B, perforin, TIA1), EBV infection of the neoplastic cells, and angiocentric growth pattern with vascular wall necrosis.[1,7]

The prognosis of ENKL is poor, with 5-year overall survival rates with traditional anthracycline containing regimens (e.g. CHOP) ± radiotherapy of 20-50%. [3,4] Part of the reason for the poor prognosis is the lack of efficacy of anthracyclines due to excretion from ENKL cells by P-glycoprotein. Chemotherapy regimens incorporating L-asparaginase such as SMILE (steroid - dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) have shown more promise.[8]

Extra-nasal ENKL represents approximately one quarter of cases.[4] The most common extranasal primary sites described in the International Peripheral T-Cell Lymphoma Project were the intestine (37%), skin (26%), testis (17%), and lung (14%).[4] CNS involvement in ENKL is rare and concomitant CNS and extranasal ENKL is particularly uncommon, with no prior reported cases to our knowledge. Here we report a patient with concomitant CNS and cutaneous ENKL who was refractory to multiple lines of therapy.

Case report

An 80-year-old Italian born woman presented with floaters in both visual fields. An initial diagnosis of bilateral anterior uveitis was made and she was treated with multiple courses of topical steroids. Six months later she was referred to a subspecialist ophthalmologist due to suboptimal clinical response. At this time, she had 6/12+ visual acuity in her right eye and less than 6/15 in her left eye. Ocular pressures were normal. On slit lamp examination there were bilateral pigmented keratic precipitates, with many bilateral vitreous cells and extensive inflammatory debris. Recent investigations for the cause of the uveitis had been negative and the ophthalmologist at this time was suspicious of intraocular lymphoma. A diagnostic-therapeutic vitrectomy of the left eye was performed. Microscopy showed scattered small lymphocytes and there were inadequate cell numbers for flow cytometry, as commonly occurs in cases of intraocular lymphoma. The visual acuity of the left eye improved from less than 6/15 to 6/7.5 two weeks later.

Shortly after, tender erythematous left leg nodules, unintentional weight loss and night sweats emerged. She was treated with antibiotics without improvement. The rash progressed to involve the trunk and fresh skin biopsy of this lesion was performed (Fig 1).

Histology : Histological examination shows moderate dermal and subcutaneous infiltrate of abnormal intermediate sized lymphocytes with irregular, hyperchromic nuclei. Epidermotropism is negligible. The subcutaneous infiltrate is reminiscent of lobular panniculitis, however, there is no significant fat rimming or necrosis. In areas, the infiltrate is predominantly peri-adnexal and perivascular with focal angioinvasion and perineural spread but without associated fibrinoid necrosis of vessel walls (Fig. 2a-b)

Immunohistochemistry : The lymphoma cells express CD2, CD3 (cytoplasmic), CD4 (partial), CD56, GATA3, TIA1, granzyme B, perforin, EBER but not for CD7, CD8, CD2, CD5, CD30, LMP1, PD1, CD303, MPO, or CD68 (Fig. 2c-f).

The patient underwent ^{18}F-flurodeoxyglucose (FDG) positron emission tomography with computed tomography (PET-CT) scan, demonstrating mostly cutaneous disease in the legs with a single mildly FDG avid mildly prominent lymph node in the left inguinal region. There was no evidence of visceral or bone marrow involvement on PET/CT, although bone marrow biopsy was not performed as she was considered to

be stage IVB on the basis of CNS (intraocular) involvement. Lumbar puncture was performed, and initial cerebrospinal fluid (CSF) cytology was reported as suspicious for leptomeningeal involvement although flow cytometry was negative. She was treated with three doses of intrathecal methotrexate, and subsequent CSF samples were negative for malignancy.

Apart from an elevated lactate dehydrogenase (2.2 x upper limit of normal) the remainder of the baseline blood tests were within normal limits and HIV and hepatitis B and C serology were negative.

The patient was treated with 2 cycles of SMILE chemotherapy, with 50% reduced doses of methotrexate, ifosfamide and etoposide complicated by fluid overload, atrioventricular nodal re-entry tachycardia requiring accessory pathway ablation, ifosfamide encephalopathy, and subsegmental pulmonary embolism in the context of L-asparaginase therapy despite anti-thrombin 3 replacement.

PET-CT post 2 cycles SMILE chemotherapy demonstrated resolution of lower leg cutaneous and left inguinal lymph node activity. Repeat lumbar puncture demonstrated no evidence of residual leptomeningeal lymphoma. There was clinical response of the cutaneous disease with residual skin pigmentation (Fig 1). Due to cumulative toxicity of therapy there was a substantial decline in performance status precluding further administration of reduced dose SMILE. As the chemotherapy administered to that point was considered insufficient to eradicate intraocular disease, binocular radiotherapy (20 Gray in 10 fractions) was administered. A highly conformal volumetric arc megavoltage external beam radiotherapy technique was utilised. Therapy was well tolerated with temporary eye dryness which responded to topical lubricant. A subjective improvement in vision was noted by the second week post therapy (she regained the ability to read).

Unfortunately, six weeks following completion of SMILE, new cutaneous lesions emerged on the back, biopsy confirmed as ENKL recurrence. Treatment with four cycles of 100mg of intravenous pembrolizumab at 3 weekly intervals failed to achieve a clinical response. Third line chemotherapy with P-GEMOX (peg-aspargase, gemcitabine, oxaliplatin) resulted in reduction in the skin lesions, however after three cycles the patient developed confusion, seizures and new focal neurological deficits. Lumbar puncture showed recurrent leptomeningeal ENKL; the patient was offered palliative care and died four days later.

Discussion

Extranodal NK/T cell lymphoma (ENKL) is a rare and aggressive form of lymphoma accounting for approximately 10% of peripheral T cell lymphoma cases internationally and 1% of lymphoma overall. [4]The typical clinical presentation is of a destructive lesion in the upper aerodigestive tract, usually in patients of Asian descent, responding well to radiotherapy in the early stages. Important adverse prognostic factors for ENKL treated with non-anthracycline based regimens are age greater than 60 years, stage III or IV disease, distant lymph-node involvement, non-nasal type disease and detectable EBV viral DNA titre. [9] While localised nasal disease typically responds to initial treatment with chemoradiotherapy, extranasal disease has consistently been shown to confer a worse prognosis and is generally treated with intensive chemotherapy. [9,10]This case describes an Australian woman of Italian ancestry who presented with cutaneous and ocular ENKL, without any nasal disease. The histology and immunohistochemistry are consistent with classically described cases, with NK cell markers, EBV positivity, cytotoxic profile and angioinvasion all present. CD3 positivity on immunohistochemistry in this case reflects cytoplasmic CD3 epsilon expression which unlike surface CD3 is usually positive in ENKL. [1]

Primary cutaneous ENKL is rare, fewer than 100 cases have been described in the literature with the majority of these being Asian patients.[11-15] The dermatological findings are varied and include subcutaneous nodules, erythematous papules, cellulitis and ulcerations which can occur at any site but appear more common at the extremities. [11-15] Radiotherapy alone is a successful treatment in localised cutaneous disease, with 80% of patients responding. For more advanced stage cutaneous disease, radiotherapy is not feasible and systemic chemotherapy is indicated.[11] The skin manifestations in this case were consistent with those described in previous case reports of primary cutaneous ENKL, with erythematous nodules and plaques predominantly in the legs. There was widespread skin involvement in more than two non-contiguous skin regions, conferring a T3 designation on the TNM staging system and significantly worse prognosis. [14]

ENKL with ocular involvement is extremely rare and only four biopsy proven case reports were identified in the medical literature.[16-19] There have been other cases described which likely represent ocular involvement, without histological evidence. [20,21] All cases described have occurred in patients with nasal ENKL as opposed to extranasal. Uveitis was the primary finding in all cases of previously described ocular ENKL, with or without retinal/choroidal detachments. [16-22] In the current case, the patient presented with recurrent uveitis and vitreous hypercellularity, with no other cause found. True CNS ENKL is extremely rare and the optimal therapy is unknown. The use of CNS penetrating agents such as high-dose methotrexate and cytarabine are the mainstay of therapy in B-cell lymphoma with CNS involvement, although these agents are challenging to deliver in very elderly patients, as highlighted by this report.

The frontline management of ENKL has moved towards asparaginase based chemotherapy. [23-27] SMILE was evaluated in a phase 2 trial of 38 patients with stage IV, relapsed or refractory ENKL demonstrating a complete response rate of 45% after 2 cycles and 1 year OS of 55%. [28] SMILE results in considerable toxicity and is challenging to deliver in elderly patients.[28,29] There is emerging evidence of the efficacy and safety of other asparaginase containing regimens such as DDGP (cisplatin, dexamethasone, gemcitabine, pegaspargase) and P-GEMOX (pegaspargase, gemcitabine and oxaliplatin) in the treatment of ENKL.[29-34] A recent randomized trial showing superior disease control and favourable toxicity for DDGP relative to SMILE represents a welcome advance for patients with this aggressive disease.[35]

The management of refractory ENKL is challenging in any patient, but particularly so in the very elderly. We elected to use the immune checkpoint inhibitor pembrolizumab on the basis of encouraging data from case reports and small case series [36-38]. Unfortunately, our patient did not derive benefit from the agent, and was effectively refractory to every therapeutic intervention apart from a brief symptomatic improvement from binocular radiotherapy. Reduced dose SMILE was poorly tolerated and limited therapy to two cycles. Based on recent randomized trial data, DDGP appears both more active and better tolerated and should be considered a preferred frontline approach. Further trials incorporating novel agents such as pembrolizumab are required to improve outcomes for patients with ENKL.

Consent: Informed consent was obtained from the patient for inclusion in this case report.

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Figure 1: Multiple confluent erythematous nodules and plaques in the lower legs and lower back at presentation (upper panel). Resolution of skin lesions with residual pigmentation following 2 cycles of SMILE chemotherapy (lower panel).

Figure 2: Skin biopsy histopathology and immunochemistry a) Diffuse dermal and subcutaneous infiltrate of lymphoma cells (H and E, x20). b) Higher magnification demonstrating medium to large in size pleomorphic lymphoma cells with hyperchromatic nuclei and irregular nuclear outlines (H and E x400) c) Strong cytoplasmic CD3 (epsilon) expression of lymphoma cells in periadnexal and perivascular distribution. d) Epstein-Barr Virus Encoded RNA (EBER) expression of lymphoma cells, including in perivascular (red arrow) and perineurial (blue arrow) distribution. e) Cytoplasmic expression of the cytotoxic protein Granzyme B by the lymphoma cell (H and E x200). f) Moderate to strong CD56 expression by the lymphoma cells (H and E x400).