Case Report

Misdiagnosed Refractory Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type, Successfully Treated: A Case Report

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Keywords

T-cell lymphoma · Natural killer/T-cell lymphoma, nasal type · Chemotherapy · Pralatrexate · Case report

Abstract

Extranodal natural killer/T-cell lymphoma (ENKL), nasal type, is a rare, aggressive non-Hodgkin lymphoma for which no clear standard of care has been established, particularly in the relapsed/refractory disease setting. Because of its rarity, randomized trials are not conducted specifically on ENKL, nasal type; however, case reports and small case series can provide important insights into potential new treatments. We present a case report of a patient with ENKL, nasal type (previously misdiagnosed as relapsing chronic sinusitis), whose disease progressed during multi-agent chemotherapy but responded to second-line treatment with single-agent pralatrexate. We discuss treatment options for relapsed/refractory ENKL, nasal type, and suggest that pralatrexate be further evaluated in this clinical setting.

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Introduction

Natural killer (NK)/T-cell lymphoma (TCL) is a rare, aggressive subtype of non-Hodgkin lymphoma (NHL) that occurs predominantly in non-nodal sites [1, 2]. Most extranodal

NK/T-cell lymphomas (ENKL) occur in the upper aerodigestive tract, such as in the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, or larynx, and are referred to as ENKL, nasal type. These locally invasive tumors are more common in Asian and South American populations than in North American and European populations [3]. Nonetheless, the diagnosis can be challenging. In many cases, the patient is initially diagnosed with chronic or recurrent sinusitis with negative neoplasm biopsies. Timely diagnosis is important, however, because the disease is aggressive, and the prognosis is typically poor, particularly once the disease recurs or becomes treatment refractory. The time of survival of patients who receive second-line therapy averages less than 5 months [2].

Pralatrexate is the first cytotoxic agent approved by the US Food and Drug Administration for the treatment of refractory or recurrent peripheral TCL [4]. Like other antifolates, pralatrexate inhibits dihydrofolate reductase, but unlike other agents, it is more efficiently internalized by the reduced folate carrier and more effectively polyglutamated, which increases intracellular retention and may explain the enhanced cytotoxicity observed in pre-clinical studies relative to methotrexate [4]. Pralatrexate has demonstrated single-agent activity against relapsed and refractory peripheral TCL (PTCL), although the ENKL subtype is not well represented in studies published to date [4–6]. Here we report what we believe to be the first successful use of pralatrexate for the treatment of a patient with ENKL, nasal type, that progressed during multi-agent, first-line chemotherapy.

Case Presentation

A 50-year-old male mestizo from a remote region of Colombia was initially referred in October 2014 for evaluation of a mass on the palate. His symptoms had first been noted in January 2014 and included anorexia, weight loss of 10.5 kg, dysphagia, progressive dyspnea, and dysphonia. He had initially been treated for chronic sinusitis with multiple courses of antibiotics and analgesics, with little improvement prior to referral. Imaging of the paranasal sinuses in May 2014 had revealed inflammation and a polyp in the right maxillary sinus, and in July 2014, neck imaging had shown bilateral chronic otomastoiditis, increased tissue in and stenosis of the nasopharynx, and a mass in the amygdaloid fossa. The adenopathy of the jugulodigastric zone measured 14 mm. In September 2014, the patient had undergone nasopharyngolaryngoscopy, which had revealed a mass originating in the palate and obstructing the right nasal cavity. The palatine tonsils were enlarged and hyperemic. The soft palate was biopsied and revealed a poorly differentiated, ulcerated, and necrotic large-cell malignant neoplasm. The immunophenotype results (CD2+, CD3+, CD16+, CD43+, CD45+, CD56+, CD57–, EBER+, granzyme B positive, TCR negative, and Ki-67+) and negative bone marrow biopsy results led to the diagnosis of ENKL, nasal type, with an Ann Arbor clinical stage of II EB extranodal.

The patient underwent tracheotomy and gastrostomy, and we initiated radiotherapy with 200–5,000 Gy to relieve the obstructed nasal cavities on October 15, 2014. Chemotherapy was initiated on December 2, 2014, and consisted of the VIPD regimen (etoposide 150 mg intravenously [IV] over 90 min, days 1–3; ifosfamide 1,800 mg IV over 60 min, days 1–3; cisplatin 50 mg IV over 60 min, days 1–3; and dexamethasone 40 mg IV, days 1–4) given every 28 days. Supportive measures included ondansetron 8 mg IV every 8 h for the first 3 days of chemotherapy, mesna 400 mg IV 0, 4, and 8 h after the start of ifosfamide, and pegfilgrastim 6 mg subcutaneously on day 5 of each cycle. The patient received 3 cycles, each complicated by febrile neutropenia and antibiotic therapy that delayed the subsequent cycle.

Despite initial improvement, disease progression was documented during the third cycle, and treatment was terminated on March 26, 2015.

We decided to use pralatrexate (30 mg/m² IV weekly for 6 weeks with 1 week of rest per cycle) as second-line therapy and initiated premedication (cyanocobalamin 1 mg intramuscularly every 8–10 weeks and folic acid 2 mg daily) on July 7, 2015, in accordance with institutional guidelines. Calcium folinate 40 mg IV was given on day 2 after every pralatrexate dose. The patient completed three 7-week cycles from July 2015 through January 21, 2016. He experienced grade 1 neutropenia (absolute neutrophil count <1,500 but >1,000 cells/mm³) on 3 occasions (July 16, September 17, and November 23, 2015). Grade 1 mucositis was treated with a magistral formulation.

The patient improved clinically during treatment (Fig. 1), and the tracheotomy tube and the gastrostomy probe were removed in October and December, 2015, respectively. His voice recovered and he made steady improvement with solid food intake and weight gain. A PET/CT scan in December 2015 revealed complete remission of the nasopharyngeal lesions, and the patient was ambulatory and free from disability. At that time, he was awaiting reconstructive surgery to improve the radiation-induced oropharyngeal fibrosis as well as allogeneic bone marrow transplantation to supplement the successful second-line therapy. However, before the transplantation could be performed, he developed dysphonia again, and pralatrexate was reinitiated on April 1, 2016. A PET scan performed in May 2016 revealed nasopharyngeal and supradiaphragmatic lesions with mediastinal compromise (Fig. 2). He ultimately received an additional 3 cycles of pralatrexate without incidents and completed treatment on August 3, 2016. A PET scan on September 26, 2016, showed diminution of metabolic activity in the supradiaphragmatic lesions. At the last follow-up, he continued to await transplantation.

Discussion

ENKL, nasal type, is a very rare and challenging diagnosis. Our patient initially presented with symptoms consistent with chronic sinusitis, which may have delayed the diagnosis. Within a year, however, he had deteriorated clinically and developed obstructive mechanical complications in both nasal cavities, structures typically affected by this disease. ENKL is radiosensitive, and we therefore began treatment with radiotherapy in hopes of debulking the tumor and providing symptom relief. Radiotherapy is an important component of initial treatment, although it should not be used alone to treat stage II disease due to a high relapse rate [1, 2].

Chemotherapy is generally used concurrently or sequentially with radiotherapy to treat sufficiently fit patients. Unlike other aggressive NHLs, ENKL, nasal type, does not respond well to anthracycline-based regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), likely due to high expression of P-glycoprotein, an ATP-dependent efflux pump that actively pumps some chemotherapy drugs out of lymphoma cells [2, 7]. We therefore used an alternative multi-agent regimen, VIPD, which has been studied as consolidation after cisplatin-based concurrent chemoradiation in this setting [8]. Unfortunately, the patient's initial partial response to treatment was not maintained, and his disease progressed before the planned 4 cycles were complete.

Given the apparent drug-refractory nature of the patient's disease, we opted to use pralatrexate as second-line treatment. At that time, pralatrexate was a relatively new option for the treatment of relapsed/refractory PTCL. In the pivotal phase II study conducted in North

America and Europe, pralatrexate produced an objective response rate of 29%, including an 11% complete response rate, in patients with relapsed/refractory PTCL [4]. A subsequent study conducted in Japan reported a 45% objective response rate, with all responses recorded within the first treatment cycle [6]. However, these studies included only 2 patients with ENKL, nasal type, too small of a subgroup to draw conclusions about the efficacy of pralatrexate in this specific TCL subtype. We were nonetheless encouraged by the drug's potential in this disease because of its increased intracellular drug retention and lack of interaction with P-glycoprotein [7, 9].

Our patient received a total of 6 cycles of pralatrexate at its recommended dose. With the first 3-cycle course, he achieved total remission of the pharyngeal lesions, which allowed for removal of the tracheotomy and nasogastric probe, return to oral feeding with excellent nutritional and weight recovery, and facilitated voice rehabilitation. His clinical outcome was excellent, and the transplantation team believes that his long-term prognosis can be improved with allogeneic bone marrow transplantation, for which he has a suitable donor and is currently awaiting treatment.

Since we initially met this patient in 2014, regimens that include L-asparaginase have increasingly been recommended as first- and/or second-line therapy [1, 2]. We cannot speculate whether such a therapy would have produced a durable remission for this patient. Given the rarity of the disease, it is unlikely that randomized trials will be conducted. Based on the rapid and complete response seen in the current case, we believe that pralatrexate warrants further evaluation and may increase the treatment options available to patients with this rare, aggressive NHL subtype.

Conclusion

Single-agent pralatrexate produced a complete response in a patient with chemotherapy-refractory ENKL, nasal type, in our clinical practice. This promising clinical activity suggests that pralatrexate may be an appropriate option for patients with relapsed/refractory ENKL, nasal type.

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Statement of Ethics

Written informed consent for publication of this paper was obtained from the patient.

Disclosure Statement

None.

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Fig. 1. Photographs of the palate before (a) and after (b) pralatrexate treatment.

Fig. 2. PET/CT scan from May 2016.