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Case Report

A Diagnostic Dilemma of Sinonasal T Cell Lymphoma: Report of A Unique Case and Literature Review

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Abstract

Background: Natural Killer/T–cell non–Hodgkin lymphomas are rare and aggressive disease of non–Hodgkin lymphoma characterized by angioinvasion, angiodestruction and necrosis. It has a strong association with Epstein–Barr virus (EBV) as the lymphoma cells are almost invariably infected with the clonal episomal form of EBV. Because of their rarity, it is a challenge to diagnose and treat them even to the experienced pathologists.

Case Presentation: The featured case describes a 40–year–old male who presented with symptoms suggestive for sinusitis. Further diagnostic investigation by the functional endoscopic sinus surgery (FESS) revealed a chronic sinusitis with multiple biopsies showing negative for malignancy, viral and bacterial infections and therefore undiagnosed for sinonasal NK/T–cell lymphoma. Subsequently after a month of surgery, he developed multiple lymph nodes in inguinal where biopsy revealed extranodal NK/T–cell non–Hodgkin lymphoma, high grade but in no time for treatment, he finally succumbed to the illness.

Conclusion: The case presented here was initially diagnosed as a chronic sinusitis, not as sinonasal NK/T–cell lymphoma which later developed into extranodal NK/T–cell lymphoma. The prognosis showed improvement for nasal lymphomas but remains poor for disseminated and extranasal lymphomas which are more aggressive with lower survival rate. It is clinically important to differentiate diseases for proper staging and monitoring as they require completely different treatment strategies.

Keywords: sinonasal, extranodal, natural killer cells, T cell, lymphoma, nasal endoscopy, Epstein Barr virus, immunotherapy

Introduction

Extranodal natural killer/T–cell non–Hodgkin lymphoma or nasal NK/T–cell non–Hodgkin lymphoma is a rare subtype of lymphoma with an aggressive course which was previously known as lethal midline granuloma. McBride first described rapid midline destruction of the face and nose in 1897. These lesions looked like necrotic granuloma macroscopically with a lethal and aggressive course, thus the name lethal midline granuloma was used for this condition (1). This disease is almost invariably associated with EBV and usually with a NK cell phenotype, a broad range of morphologic appearances with frequent necrosis and angioinvasion. It usually starts extranodally where it can be present in the nose, nasopharynx, paranasal sinus, tonsils and sometimes in palate collectively referred as nasal NK/T–cell lymphoma. Rarely, the lymphoma can be disseminated on presentation, with infiltration of the liver, spleen, skin, lymph nodes, and bone marrow referred as non–nasal NK/T–cell lymphoma (2). Involvement of peripheral blood is frequently found. These cases are referred to as aggressive NK–cell leukemia/lymphoma with EBV positive in predominant majority (3).

Rare destructive midline facial lesions are referred to as lethal midline granuloma. It consists of three histological types of lethal midline granuloma namely the Wegener’s
granulomatosis with generalized necrotizing vasculitis, the polymorphic reticulosis with proliferation of atypical large cell with multi or mononucleated, plasma cells, macrophages, neutrophils, lymphocytes and lastly the NK/T−cell lymphoma when proliferating cells becomes immunoreactively positive to polyclonal antibodies against T−cells(2,4).

Lymphomas constitute 3−5% of all malignancies and non−Hodgkin lymphoma, a cancer that arises in the nodal and extranodal lymphoid tissue constitutes around 60% of all lymphomas(5). NK/T−cell lymphomas are accounted for 15−25% of all lymphomas in the Asia(6), most common in China, Japan, Korea, Hong Kong and in native populations of Central and South American (e.g. Peru and Mexico) than in the Western populations(6,8).

The most common presenting symptoms of sinonasal malignancies are nasal obstruction, swelling and discharge, localized pain (e.g. left−sided nasal), sore throat, epistaxis and headache. However, these symptoms are nonspecific especially in distinguishing between non−Hodgkin lymphomas and squamous cell carcinoma (SCC), as SCC is the most frequent malignant tumour in the sinonasal cavity (40% to 50% of all sinonasal malignancies) whereas non−Hodgkin lymphomas are the second most frequent(7). On the other hand, extranodal NK/T−cell non−Hodgkin lymphoma is often confused with lymphomatoid granulomatosis due to their angiocentric nature and extranodal localization. However, EBV−infected B cells in lymphomatoid granulomatosis is the main distinction of these two pathologic entities(8).

Here we report a rare case of NK/T cell non−Hodgkin lymphoma with much difficulty to diagnose. Besides highlighting the immunological aspects of sinonasal NK/T−cell lymphoma, we also review on the diagnosis of these malignancies as it is clinically important because they require completely different treatment strategies. The case has been prepared according to the guidelines for medical case reports described by Gagnier et al.(9).

**Case Presentation**

On 21st May 2016, a 40−year−old male presented with severe left sided nasal congestion with posterior nasal drip that has been bothering him for the past three months. Patient additionally reported of having soreness of the throat with odynophagia. He was previously treated symptomatically at the local clinics with no improvements. Social history was notable for tobacco use with no alcohol abuse previously. Past medical history was unremarkable and family history was not significant for any condition or malignancy. During examination on his first visit to our clinic, he appeared comfortable with no respiratory distress, and his vitals were stable. Physical examination was notable for sinusitis. There was a minimal crusting seen on bilateral anterior rhinoscopy. Intraorally, noted pus trickling down on the posterior pharyngeal wall, while other subsites such as buccal mucosa, alveolus, gingiva, hard palate, tongue and floor of mouth were normal. His nasal endoscopy showed bilateral inferior turbinate hypertrophy and congested osteomeatal complex bilaterally with pus discharging into the posterior nasal space. He was then treated for sinusitis with an oral course of ampicillin sulbactam 375mg twice a day and intranasal beclomethasone nasal spray two puffs twice a day.

He underwent contrast−enhanced computed tomography of the brain, paranasal sinus and neck which revealed pansinusitis. There was no definite mass seen in the paranasal sinus or the posterior nasal space. There were few nodes on both sides of the neck and supraclavicular region measuring 3−6mm. He was then planned for functional endoscopic sinus surgery (FESS) and intra−operatively it was noted that the septal, maxillary and ethmoidal mucosa were polypoidal with no evident pus or mass. Swab specimens were taken for culture and sensitivity, fungal culture and tuberculosis culture which were reported negative. Biopsies were taken from the polypoidal mucosa of the left nasal septum, left uncinate process, left ethmoidal tissue and posterior nasal space which was later reported as inflamed granulation tissue with necrotic tissue consistent with chronic sinusitis features. There was no evidence of granuloma, fungal bodies or malignancy.

One month after the surgery, patient developed a sudden flare of sinusitis with facial pain, facial fullness and copious amount of nasal discharge, thick and yellow. He also had a high spiking temperature. He was admitted for intravenous antibiotics, cefuroxime and metronidazole. His nasal endoscopy revealed slough with crusting the septum and inferior turbinates extending to the posterior pharyngeal wall posteroinferiorly and tissue were obtained for fungal studies which were reported negative. Biopsies were taken from the polypoidal mucosa of the left nasal septum, left uncinate process, left ethmoidal tissue and posterior nasal space which was later reported as inflamed granulation tissue with necrotic tissue consistent with chronic sinusitis features. There was no evidence of granuloma, fungal bodies or malignancy.

As shown in Figure 1A, his full blood picture showed severe anisopoikilocytosis with hypochromic microcytic cells. The ovalocytes, elliptocytes, pencil tears, tear drop, and target cells were seen with few oval macrocytes. No immature white cells and no platelet clumping were
noted. Even though there were no obvious signs of upper and lower gastro-intestinal tract bleeding, his stool was positive for occult bleeding and with the decreasing trend of haemoglobin counts, he was referred to surgical team and underwent oesophagastroduodenoscopy, but there was no active bleeding noted endoscopically. He also developed balanitis and was seen by the urology team.

In the midst of establishing his diagnosis, he underwent another contrast enhance computer tomography of neck, thorax, abdomen and pelvis which revealed cervical, axillary, mediastinal and inguinal lymphadenopathy with multiple bilateral lung nodules and pleural effusion. In addition, excision biopsy of the inguinal nodes was performed by the surgical team under local anaesthesia. Upon investigation, he also developed cutaneous ulcer lesions on the chest region. By this time, patient’s condition was already deteriorating. He was looking septic with worsening pneumonia and his antibiotics were escalated to intravenous etarpenem. He then developed sudden onset of acute respiratory distress in the ward and was opted for mechanical ventilation via endotracheal intubation. He was only ventilated for two days before he succumbed to the disease after the long battle. A postmortem examination was not permitted by the family. Only after his passing, the biopsy of the inguinal lymph node was reported as consistent with NK/T-cell non-Hodgkin lymphoma, high grade. The tumour cells were positive for CD3, CD45, CD56 and few for CD30 stains with Ki-67 of 80-85% (Figure 1B-E).

**Discussion**

Extranodal NK/T-cell lymphomas are commonly found in adults but may present in children as well. The condition is estimated to be present in roughly <1% of all non-Hodgkin lymphomas in the Western World and up to 10% in Asia and South America. There are studies reporting the predominance of a male to female with ratio of 2:1 to 3:1. Majority of these cases (around two-thirds) are diagnosed in stage I/II of the disease in the upper aerodigestive tract mainly.

Patient with the extranodal NK/T-cell lymphoma usually presents with localized nasal symptoms including nasal congestion and persistent nasal discharge. Constitutional symptoms may follow such as weight loss, night sweats and unexplained fever. It usually involves the nose, nasopharynx, paranasal sinus, Waldeyer’s ring and the tonsils. Sometimes, the nasal lesions can erode the floor of the nose causing a perforation on the hard palate. Our patient did present with nasal symptoms, but there was no mass or lesion on endoscopy that was suggesting anything else but sinusitis. Of note, it is important to undergo F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan for accurate staging especially for newly diagnosed patients with lymphomas to avoid any of the misdiagnoses of lymphomas as misdiagnose and misclassifications can have serious consequences in terms of treatment. However, his results from computed tomography also suggested sinusitis. In addition, as there is a strong association with EBV, a quantification of plasma EBV DNA is mandatory for useful monitoring and prognostication as it gives an accurate measurement of the lymphoma load. In our case, the patient was not screened for EBV as his clinical history did not suggest a prolonged period of illness which may result in elevated EBV antibodies. Therefore, treatment strategies were based on chronic sinusitis without any benefit on patients.

The disease may disseminate to other sites such as skin, testis and gastrointestinal tract as well. Moreover, it could also cause rashes, hepatosplenomegaly, lymphadenopathy, and hyperferritinemia. Studies reported that in the marrow and some other organs it was found active haemophagocytosis, which refers to this disease also, and often the median survival in these cases estimated to be several weeks or months. In rare occasions, the primary site of the lymphoma may not be nasal, which also known as non–nasal NK/T–cell lymphomas and this types are known to be more aggressive with poor survival rate and adverse clinical characteristics. Normally, to assess the tumour extent in the nasal area, CT imaging and magnetic resonance imaging (MRI) are useful; CT gives information on the bony part and MRI gives on the soft tissue part. CT and MRI are not able to detect the absence of occult involvement in the nasal area. To define non–nasal T–cell lymphomas, it is necessary to have absence of involvement in nasal region by using PET/CT scan. Even though our patient presented with nasal symptoms, there wasn’t an obvious mass for biopsy, and nasal tissue biopsies were negative for any malignancy. His CT scan showed sinusitis evidence which correlated with his nasal symptoms. The PET/CT scan is usually used to determine if the non–nasal lymphomas are associated with nasal primaries indicating them as disseminated nasal lymphomas. The disseminated aggressive T–cell lymphoma can involve the bone marrow and peripheral blood with fulminant systemic dissemination such as in our patient when he presented with pancytopenia.

Compared to the nodal type of lymphomas, the extranodal type is a challenge to identify due to the scanty biopsy obtained not providing an accurate diagnosis. Furthermore, there are many contributory factors to these challenges, including the expansion of extranodal lymphoma subtypes, the variation in clinical features, morphology, genetics, immunophenotype, and
Figure 1: Histopathology of a case of sinonasal NK/T cell lymphoma. (A) haematoxylin eosin (H&E) stain of inguinal lymph nodes biopsy in high power field shows abnormal–lymphoid cells (large–transformed lymphocytes, arrow) (original magnification, x200). Immunostaining for (B) CD3, (C) CD56, (D) CD45RO showing abundant–positive lymphoma cells (original magnification, x200). (E) Immunostaining for Ki–67. More than 80% of lymphatic cells showed a positive nuclear immunoreaction for Ki–67 (original magnification, x200).
the obstacles in discrimination of extranodal lymphomas from neoplasms and especially with the reactive lymphoid infiltrates.

The most specific immunophenotyping of extranodal T cell lymphoma is CD2+, CD56+, and cells with intracytoplasmic expression of anti-CD3 antibody. They also express negative of CD3 on the cell surface (sCD3−), cytoplasmic CD3ε+, and cytotoxic molecules such as granzyme B, T-cell intracellular antigen 1, perforin and TIA1. Molecular biology studies also detected EBV DNA expression in the tumour cell.

There are various modality of treatment for patients with T-cell lymphoma varying from chemotherapy regimens and radiotherapy according to their staging. Previously, patients were treated with anthracycline-containing CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone) or CHOP like regimens but they worked poorly due to the multidrug resistance P–glycoprotein on NK cells. Radiotherapy is given as a first line treatment in stage I/II of the disease with a combination of chemotherapy either as a concurrent treatment or as a sequential treatment, by using non–anthracycline regimens especially those containing L–asparaginase. The use of radiotherapy alone was related with a high incidence of systemic relapse accounting for 18.8% in a retrospective analysis and even with the addition of CHOP did not improve the outcome. However, radiotherapy alone can be administered for cases where chemotherapy is unsafe and in older patients with poor performance status. On the other hand, the function of radiotherapy in salvage still need more investigation; some studies showed that the use of radiotherapy with newly diagnosed advanced extranodal natural killer/T-cell lymphoma is not associated with an overall survival rate in patients.

In East Asia (mainly), for newly diagnosed advance stage III and stage IV diseases, the standard chemotherapy regimen is SMILE (steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase and etoposide), which was followed by radiotherapy or could be used as sandwich chemoradiotherapy. For relapsed or refractory cases of T-cell lymphoma, SMILE or similar regimen are the only effective chemotherapeutic that has been confirmed by clinical trials; in a study conducted on a total of 38 patients in newly diagnosed stage IV extranodal natural killer/T-cell lymphoma, after 2 cycles, the overall response rate was 79%, the complete response rate was 45%. As well, another study reported that the 5–year overall survival rate for similar cases was 45%.

Furthermore, there are some other novel immunotherapy options that emerged during the recent years, including targeting each of CD30, CD38, PD1, and EBV antigens. CD30 is a cellular membrane protein of the tumour necrosis factor receptor (TNFRSF8), it is solely expressed in tumour cells and not in normal cells, but its significance in extranodal NK/T-Cell lymphoma is still argumentative with paucity of the studies; its expression in four different studies were variable with contrasting results if it is significant or non–significant. Although some studies showed high efficacy for using CD30–targeted antibodies in T cell lymphomas as CD30 antibodies works directly by immune activation or by internalization of synthetic antineoplastic toxic agent, targeting CD30 has not been proven as a complete effective immunotherapy option for NK/T–Cell lymphomas. On the other hand, a case report in 2016 has investigated the role of daratumumab (anti–CD38 antibodies) in enhancing the effectiveness of antibody–associate cellular and complement–associate cytotoxicity in cellular CD38 expression; CD38 is a glycoprotein expressed in several immune cells, especially in NK cells and B cells. This report showed that in the first 5 weeks of using daratumumab, there was an increased EBV titers, but it was followed by a continuous reduction in the titers and was concluded with undetectable virus. However, further studies in using anti–CD38 antibodies in NK/T–Cell lymphomas are still needed.

Recently, relapsed patients with previously failing chemotherapy are treated with an anti–PD1 monoclonal antibody called pembrolizumab (a humanized IgG4 antagonistic anti–PD1 mAb). Programmed death protein ligand 1 (PDL1) are expressed on T–cell lymphoma cells and are associated with EBV infections where PDL1 expressions are upregulated by EBV latent membrane protein 1. The PDL1 expressions attached to the inhibitory receptors PD1 of T–effector cells suppressing the T–cell activity thus enabling the evasion of T–cell lymphoma. Moreover, a study showed that through autologous T–cell activation after bone marrow transplantation, researchers have designed an initial EBV antigen targeting EBV–associated extranodal NK/T–Cell lymphoma; EBV increases the expression of latent membrane protein 1 and 2 (LMP1 and LMP2) and induces NF–κB/MAPK pathways.

Besides this, autologous and allogeneic haematopoietic stem cell transplantation is also used in high risk patients for relapse or refractory and for advance cases. Intravenous infusions of stem cells collected from peripheral blood, bone marrow and umbilical cord blood are used to provide a hematopoietic function in patients with defective immune system and damaged bone marrow. However, uses of hematopoietic stem cell transplantation in the treatment of natural killer/T–cell lymphomas are still an argumentative issue due to inability to provide...
enough randomized controlled experiments. In aggressive T–cell lymphoma, there are studies with patients treated with SMILE regimen followed by allogeneic hematopoietic stem cells transplantation showing significant survival rates (38). Although there are several studies that showed the efficacy of allogeneic hematopoietic stem cells transplantation in the treatment of extranodal NK/T–Cell lymphoma, its use remains limited due to its high rate of treatment–associated mortality (39). Moreover, retrospective studies that compared autologous and allogeneic haematopoietic stem cell transplantation in extranodal NK/T-Cell lymphoma cases have found that autologous yielded a better significant overall survival compared to allogeneic (40). Considering the high cost with the expected results of haematopoietic stem cell transplantation, its treatment efficacy needs further research to gain a higher stage of trust.

**Conclusion**

The initial presentation of this case was diagnosed as chronic sinusitis that was later re–established as extranodal NK/T–cell lymphoma. T–cell lymphoma has a rare incidence thus experience in diagnosing and staging the disease is limited. The prognosis of the disease showed improvement for local nasal lymphomas but remains poor for non–nasal NK/T–cell lymphomas and disseminated lymphomas. The disease should be diagnosed and staged appropriately to achieve the effectiveness of the treatment. Although immunotherapy options are still limited and under development to date, the results are promising for future treatment of NK/T–cell lymphomas, as it has lower side effects while being less harmful and cost effective compared to other available treatment options.

**References**


