Review Article

Extranodal Nasofacial Natural Killer/T-Cell Lymphoma Often Missed by Clinician

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Abstract

Aim: This study aims to review the current literature and to focus on etiopathogenesis, clinical profile, diagnosis, and treatment of extranodal nasofacial natural killer (NK)/T-cell lymphoma. **Materials and Methods:** It is based upon the available literatures from PubMed, Scopus, and Google scholar with the keywords: etiopathogenesis, clinical pictures, diagnostic methods, and current treatment of extranodal nasofacial NK/T-cell lymphoma from 2002 to 2017. **Results:** Primary nasofacial lymphoma is a rare form of malignancy in head and neck area. Extranodal nasofacial NK/T-cell lymphoma is an unusual clinical entity, which is an aggressive entity of non-Hodgkin's lymphoma with distinct clinicopathological pictures. It is possibly associated with Epstein–Barr virus infection. It is highly aggressive disease with poor prognosis. Nasofacial NK/T-cell lymphoma or lethal midline granuloma is often associated with destruction of midface and surrounding areas such as orbit, paranasal sinuses, and palate. The clinical picture is highly variable, often missed by clinician and depends on location and histopathological type of the lesion. Histopathological and immunohistochemistry are important tools for diagnosis of nasofacial NK/T-cell lymphoma. Histopathological picture shows angiocentric and angiodestructive pattern of tumor cells which often mimic vasculitis. Radiotherapy is the treatment of choice which improves quality and longevity of life whereas addition of chemotherapy gives additional benefit to the patients. **Conclusion:** Practicing physicians and otorhinolaryngologist need to be aware of this nonspecific presentation of lesion to prevent delay in diagnosis. Early diagnosis and intervention prolongs the survival of the patients.

Keywords: Chemotherapy, nasofacial, natural killer/T-cell lymphoma, radiotherapy, sinonasal area

Introduction

Nasofacial natural killer (NK)/T-cell lymphoma is a midfacial necrotizing lesion, characterized by granulomatous tissue with destruction of the mucosa of the upper aerodigestive tract. It is newly recognized clinical entity of non-Hodgkin's lymphoma. This lesion is now definitively categorized in the World Health Organization lymphoma classification system as nasal or sinonasal type extranodal NK/T-cell lymphoma (ENKTCL). It is common in those of Asian origin whereas rare in western population.[1] ENKTCL of nasofacial area causes necrosis with involvement of midfacial bone causing centrifugal destruction of mid facial area with no tendency for healing. The etiopathogenesis is unknown but it is related to Epstein–Barr virus (EBV) infection, which is often associated with poor prognosis.[2] It is difficult to diagnose because of the wide array of similar pathology and nonspecific symptoms. The different terminology used for this diseases are Stewart's granuloma, lethal midline granuloma, idiopathic midline granuloma, idiopathic midline destructive disease, midline nonhealing granuloma, polymorphic reticulosis, and lymphomatoid granulomatosis.[3] It occurs around the fourth decades of life, and male to female ratio is 8:1 to 2:1.[3] Common sites for nasofacial or sinonasal NK/T-cell lymphomas are the maxillary sinus, nasopharynx, oropharynx, palate, oral cavity, tonsils, and hypopharynx.[4] Clinical manifestations

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vary according to the site being affected. The common clinical findings to all such lesions are the progression of ulceration or vegetative process to destruction of nasofacial region, resulting in functional and cosmetic deformity.[5] Nasofacial NK/T-cell lymphoma is aggressive, locally destructive, and necrotic lesion of the midfacial area. The differential diagnoses of this NK/T-cell lymphoma of nasofacial region are Wegener's granuloma and epidermoid carcinoma.

Materials and Methods

It is based on the available literatures from PubMed, Scopus, and Google scholar with the keywords: epidemiology, etiopathogenesis, clinical pictures, diagnostic methods, and current treatment of extranodal nasofacial NK/T-cell lymphoma from the last 15 years' data.

Results

Isolated nasofacial lymphoma is a rare form of malignancy in head and neck area. It can occur at any age but usually affects patients during the fourth to fifth decades. Extranodal nasofacial NK/T-cell lymphoma is an aggressive type of non-Hodgkin's lymphoma with distinct clinicopathological presentations. It has poor prognosis. Nasofacial NK/T-cell lymphoma or lethal midline granuloma often causes destruction of midface and surrounding areas such as orbit, paranasal sinuses, and palate. The clinical features are highly variable, often missed by clinician and depend on location and histopathological type of the lesion. Histopathological and immunohistochemistry are important tools for diagnosis of nasofacial NK/T-cell lymphoma. Histopathological findings show angiocentric distribution of tumor cells and angiodestruction which often mimic vasculitis. Radiotherapy is the treatment of choice which enhances the quality and longevity of life whereas addition of chemotherapy gives additional benefit to the patient and quality of life.

Discussion

Epidemiology

Nasofacial NK/T-cell lymphoma is a rare clinical entity, but often seen in Asia, Mexico, and South America than North America and Europe.[6] ENKTCL is seen in all parts of the world, although commonly seen in southeast countries (like Japan, china, Taiwan, Korea, Thailand, and Hong Kong), Mesoamerica (Guatemala and Mexico), and southern America (Brazil and Peru).[7] It is rare in Europe and USA. Extranodal nasofacial NK/T-cell lymphoma accounts for 10% of all non-Hodgkin's lymphoma in Asia and Latin America, but only for 1% in Europe and North America.[8] It accounts for 75% of lymphoma originating within sinonasal area in Korea. In India, ENKTCL is rarely seen.[9]

Etiopathogenesis

ENKTCL is a type of non-Hodgkin's lymphoma, mostly arises from NK cells and only a few from cytotoxic T-cells.[10] EBV may be the cause of ENKTCL where EBV DNA is seen in the lesional tissue.[11] Hypersensitivity to mosquito bite has association with EBV infection and NK/T-cell lymphoma.[12] Recently, it is explained that mosquito bites can induce expression of a viral oncogene LMP1 in NK-cell via mosquito antigen-specific CD4+ T-cells, which may cause oncogenesis of NK-cells.[13] Mature or peripheral NK/T-cell lymphomas constitute 10%–15% of all non-Hodgkin's lymphoma, and out of them, natural-type NK/T-cell lymphoma is the most common type. Now, this variety is referred to as angiocentric lymphoma in the Revised European American Lymphoma classification or as nasal NK/T-cell lymphoma by the World Health organization-European Organization for Research and Treatment of Cancer classification.[14] Some suggest that EBV may play important role in the development of NK/T-cell lymphoma.[15]

Genetic abnormality

Fas (Apo-1/CD95) is an apoptosis-signaling cell surface receptor belonging to the tumor necrosis factor receptor, and it acts as tumor suppressor gene. Mutation with Fas gene may initiate ENKTCL. Mutation of tumor suppressor gene p53 has been seen in 48% of ENKTCL.[16] Downregulation of Class-I human leukocyte antigen (HLA) antigens thought to arise in NK/T-cell lymphoma.

Clinical profile

Nasofacial NK/T-cell lymphomas are aggressive, locally destructive lesion of the mid facial area [Figure 1]. It is a rare clinicopathological entity characterized by necrotic process arising in the sinonasal cavity and extending to the midfacial area with centrifugal destruction of the nasal bone. It is also called as polymorphic reticulosis, midline malignant reticulosis, Stewart's granuloma, and NK/T-cell lymphoma.[17] Onset of this disease is usually fifth decade of life in western country[18] whereas in Asia, patients are young with mean age of 40 years and male predominance.[2] The nonspecific clinical symptom is a major obstacle in early diagnosis and management of this lesion. Clinical presentations of nasofacial ENKTCL vary according to location and histopathological

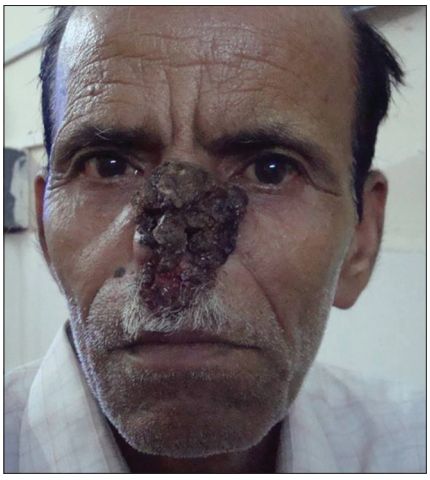

Figure 1: Midfacial destruction in extranodal natural killer/T-cell lymphoma of nasofacial area

type of the lesion. Physicians and otorhinolaryngologist should be aware about clinical manifestations for early and optimal treatment. ENKTCL affecting nasofacial area causes granulomatous-like lesion over midfacial area.[19] This destructive lesion slowly affects adjacent tissue such as paranasal sinuses, eye, oral cavity and skin. The nose is the most commonly affected in midfacial area. Nasal septal perforation with mutilation of the surrounding tissues often occurs.[20] The most common symptoms are nasal stuffiness with or without nasal discharge. Patients may present with blood-stained nasal discharge, nasal obstruction, nasal septal perforation, oroantral fistula, and cosmetically facial deformity. The rapidly spreading lesion can cause large fungating mass over face.[21] It can affect the paranasal sinuses like maxillary sinuses followed by ethmoidal and frontal while sphenoid sinus is rarely affected. Orbital involvement causes swelling and edema of the orbit. Orbital invasion occurs through destruction of floor and medial wall of the orbit. Visual acuity is affected due to consequences of uveitis, vitritis, orbital invasion, and cranial nerve involvement.[22] ENKTCL rarely arises from the oral cavity. The lesions in the nose and paranasal sinuses can extend to the hard and soft palate, uvula, posterior pharyngeal wall, and base of tongue.[23] Patient presents with foul smell from intraoral necrotic ulcerations.

Diagnosis

Early diagnosis of ENKTCL is needed to prevent spread of the disease and to prevent complications. The surface of the affected site is associated with crusting and necrotic tissue, so the diagnosis of NK/T-cell lymphoma is extremely difficult by taking only punch biopsy. This difficulty may explain why some clinician misses the diagnosis. Excisional biopsy or deep biopsy is often essential for the diagnosis of the lesion. The diagnosis of midfacial NK/T-cell lymphoma is based on the histopathological picture, immunophenotype of the atypical cells, and the analysis of T-cell receptor genes.[24] The characteristic histopathological picture in NK/T-cell lymphoma shows angiocentric and angiodestructive growth pattern with zonal necrosis [Figure 2a and b]. Immunohistochemical study shows positive CD3, CD43, CD45RO, CD20, and CD57 and demonstrates that the atypical lymphoid cells have T-cell phenotype.[25] Nasal variety of NK/T-cell lymphoma reveals specific characteristics of NK-cells. NK-cells are phagocytic cells, act against tumor cells and cell affected with bacteria and viruses without prior sensitization. A bipotential progenitor cells in the bone marrow differentiate into T- and NK-cells. NK-cells commonly appear as small lymphocytes with azurophilic granules and immunophenotypically express the characteristic CD56 marker [Figure 3]. As a common ontogeny with T-cells, NK-cells express some T-cell markers. Nasal NK/T-cell lymphomas have a predilection for nasal cavity and upper part of aerodigestive tract. They also affect skin and soft tissue in nasofacial area. Elderly males with age group of above 50 years are usually affected. The clinical presentation varies according to the location and histopathological type. The most common clinical presentation is chronic nasal obstruction or a purulent nasal discharge.[24] The necrotic lesions mimic to other granulomatous lesions and sometimes difficult to diagnose because of the nonspecific symptoms and often require multiple biopsies for the confirmed diagnosis. Gross appearance of the lesion is usually looking like necrotic granuloma with ulcerations and destruction of nose and sinuses with destruction of soft tissue, cartilage, and bone. Ulcerations at nasal cavity or oral cavity along with conjunctivitis may occur. Radiological findings in computed tomography scan and magnetic resonance imaging are not distinctive for other malignant lesions, typically showing irregular margins, bone destruction, and heterogeneous contrast enhancement. Histopathological examination revealed tissue necrosis and infiltration with mixture of small, medium, and large size lymphoid cells. Immunohistochemical study revealed that these abnormal lymphoid cells are CD2+, CD3, CD4, CD4−, CD5−, CD15−, and CD56+.The most common immunophenotype are CD56+, CD2+, and surface CD2−.[26] EBV RNA is seen in 80%–100% cases of NK/T-cell lymphoma whereas less often (15%–40%) present in nasal type of NK/T-cell lymphoma cases.[27]

Treatment options

Treatment of NK/T-cell lymphoma in nasofacial area is not well codified, and it depends on the stage of disease. Some suggest the use of anthracycline-based polychemotherapy followed by external radiation for patients younger than 60 years of age whereas the same association but without anthracycline in older patients.[6] Others still advice radiotherapy alone in less advanced stage of the disease as failure rate with chemotherapy alone is around 40%. Radiotherapy after failure cases of chemotherapy causes improvement of

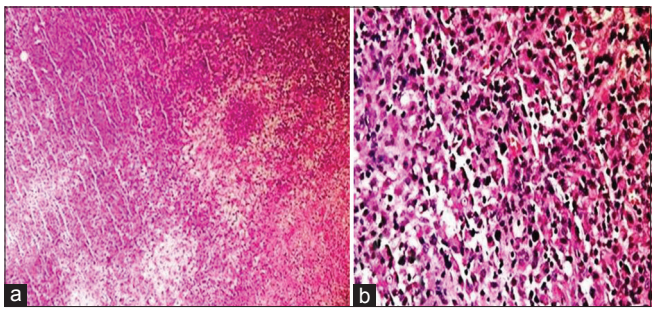

Figure 2: (a) Photomicrograph showing extensive necrosis (H and E, ×100) and (b) atypical lymphocytes, plasma cells, histiocytes, and eosinophils (H and E, ×400)

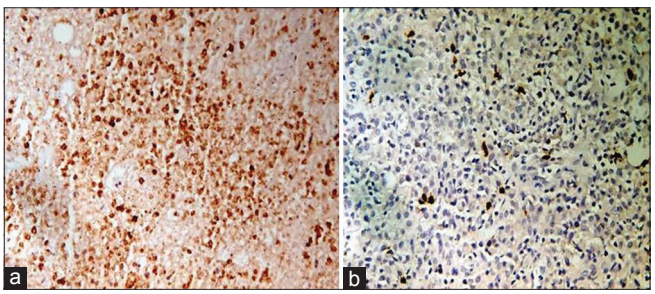

Figure 3: (a) Immunohistochemistry lymphocytes positive for CD56 and (b) with CD3 (H and E, ×100)

prognosis.[28] Overall survival of patients with all treatment is around 37%.[29] Localized ENKTCL of nasofacial area responds well to radiotherapy. Radiotherapy has greatest benefit if given early and lesion is localized.[30] About 20%–30% patients treated with radiotherapy alone has chance of failure in extranodal site,[31] and local recurrence rate ranges from 31% to 67%.[32] Chemotherapy in local disease reduces the chances of recurrence and systemic dissemination. Current chemotherapeutic regimes are reserved for control of micrometastases following radiotherapy.[18] When this tumor is invading the surroundings soft tissue and bony part, radiotherapy should be added with chemotherapy. As in other tumor, positive clinical outcome is achieved with early treatment. Treatment of sinonasal NK/T-cell lymphoma is done by the CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate) chemotherapy and radiotherapy.[25] This disease has poor outcome. The prognosis of NK/T-cell lymphoma is extremely poor, if it is associated with systemic involvement. Better prognosis is expected with early and accurate diagnosis along with aggressive treatment with chemotherapy and radiotherapy. Combined chemotherapy followed by external beam radiation is beneficial in patients and have good survival rate.[33] Nasal NK/T-cell lymphoma is an aggressive lesion with rapid downhill progression. It can cause high mortality if not treated timely. The high mortality is due to septicemia, invasion into blood vessels or into brain leading to abscess formation.

Prognosis

ENKTCL is an aggressive disease with worst prognosis if not treated early. The 5-year survival ranges from 37.9% to 45.3%.[34] Degree of angiocentricity, EBV load, and stage of disease using Ann Arbor staging have been evaluated to evaluate potential predictors for poor outcome.[35]

Conclusion

Nasofacial location of NK/T-cell lymphoma is rarely seen. The confusing clinical profile of this disease often creates suspicion for exact diagnosis. Diagnosis is based on the biopsy and immunohistochemistry. Immunohistochemistry is always mandatory to diagnose this disease and its treatment. Early diagnosis and intervention prolongs the survival of the patients. Treatment needs combined chemo and radiotherapy. This disease carries an overall poor prognosis with midline destruction of soft tissue at nasofacial area with very aggressive pattern of spread. Optimal management of NK/T-cell lymphoma in nasofacial area must be based on multidisciplinary approach among otorhinolaryngologist, hemato-oncologist, and radiation oncologist for best outcome. Practicing physicians need to be aware of these nonspecific presentations of this lesion for not missing the diagnosis and to start early treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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