

Primary nasopharyngeal interdigitating dendritic cell tumor presentation and response to radiation therapy

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Abstract

We report the case of a primary nasopharyngeal interdigitating dendritic cell tumor (IDDC). A 25-year old male presented with bilateral decreased hearing, double vision, and ataxia. Flexible nasopharyngoscopy reviewed a large mass obstructing and filling the entire nasopharynx. MRI and PET-CT confirmed the presence of the primary tumor and demonstrated bilateral cervical lymphadenopathy. Biopsy of the nasopharynx revealed a hematolymphoid neoplasm with dendritic cell differentiation, most consistent with an IDDC. The lesion was unresectable. The patient was treated with definitive radiotherapy to 66 Gy to the primary tumor and 50 Gy to the bilateral cervical lymphatics using an IMRT technique. A complete response was achieved and the patient remains disease free at the primary site 23 months after completion of radiotherapy.

Case Report

A 25-year old previously healthy African American male presented with a one month history of bilateral decreased hearing, double vision, and ataxia. He was initially diagnosed with vertigo and started on meclizine without relief of symptoms. His symptoms progressed rapidly over four weeks to include right-sided facial weakness, sensation loss and decreased taste. Physical examination revealed palsies of the right cranial nerve VI, decreased sensation in the right V3 branch of the trigeminal nerve, right cranial nerve VII. Bilateral middle ear effusions were present. Palpation of the neck revealed a 6x8 cm firm nodal mass in the left

level II-V cervical levels and a firm 2 cm right level II lymph node. Flexible fiberoptic endoscopy demonstrated a large mass obstructing and filling the entire nasopharynx.

Staging radiographic findings

A head MRI was obtained. T1 post-contrast sequences showed a lobulated and heterogeneously enhancing mass with regions of necrosis filling the nasopharynx extending to the clivus and along the right carotid canal to involve the right cavernous sinus, Meckel's cave and the adjacent tentorial dura. Pathologically enlarged bilateral lymph nodes were seen, some of which demonstrated heterogeneous T2 signal hyperintensity and T1 hypointensity suggestive of necrosis. A whole body PET-CT scan (Figure 1) revealed a hypodense mass in the right nasopharynx with increased 18F-fluorodeoxy-glucose (FDG) uptake with a maximum standard uptake value (SUV) of 11.7 and an average SUV of 9.4. Additionally, bilateral palpable cervical adenopathy contained increased FDG uptake with maximum SUVs ranging from 5.5-10.1 and average SUVs of 4.7-8.6. The patient was staged with a T4B, N3B, M0, stage IVB, nasopharyngeal malignancy according to the AJCC Edition 6 staging guidelines.

Pathological findings

The patient was taken to the operating room for direct nasopharyngoscopy with biopsy. The operative findings demonstrated a large exophytic and necrotic mass in the nasopharynx. Histology demonstrated a diffuse infiltrate of large pleomorphic cells with moderate eosinophilic cytoplasm, folded nuclei and occasionally prominent nucleoli. Mitotic figures were easily identified and there were areas of necrosis present. There was a background of small lymphoid cells. Immunohistochemical stains of the neoplastic cell population revealed the tumor to be CD43 and S100 positive, CD45 weakly positive, and CD68 and myeloperoxidase had focal weak positivity. All other stains including CD3, CD4, CD5, CD7, CD56, TIA-1, UCHL-1, CD30, Alk1, CD19, CD20, CD21, 4KB5, CD31, CD34, CD35, lysozyme, Leder, mela, HMB45, keratin, EBER and c-kit were negative. Gene rearrangement studies were performed showing no evidence of clonal immunoglobulin heavy chain gene rearrangement but there was a peak suggestive of a T-cell receptor gamma chain gene rearrangement. The neoplasm was classified as a hematolymphoid neoplasm with dendritic cell differentiation, most consistent with an interdigitating dendritic cell tumor (IDDC) (Figure 2).

Initial therapeutic intervention

The patient was started on oral dexamethasone 2 mg twice daily for a period of one week

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followed by a three week taper. His cranial neuropathies resolved completely within a few days. The patient underwent Image Guided Intensity Modulated Radiation Therapy (IG-IMRT) on a Hi-Art Helical Tomotherapy (Madison, WI) unit. The target volume included the gross disease in the skull base, nasopharynx, the bilateral cervical lymph nodes and the retropharyngeal lymph nodes, and was prescribed 50 Gy in 25 fractions (Figure 3). The patient had a complete clinical response. A repeat MRI scan obtained after the initial 50 Gy demonstrated an 80% decrease in the size of the primary tumor and nodal disease. An additional 16 Gy in 8 fractions was prescribed to the initial extent of primary and nodal disease for a total dose of 66 Gy delivered in 33 fractions over a course of 6.5 weeks. The patient tolerated the treatment well but developed grade 2 nausea requiring anti-emetics, and grade 2 radiation-induced xerostomia, mucositis, and dermatitis. One month following radiation the patient was started on systemic chemotherapy with ifosfamide (5 mg/m²), carboplatin (AUC 5) and etoposide (100 mg/m²) and mesna (5 mg/m²), receiving a total of 4 cycles. He also received central nervous system (CNS) prophylaxis with intrathecal methotrexate (12 mg) for a total of 3 cycles.

Radiographic response assessment

A repeat whole body PET-CT scan obtained one month after completion of external beam radiotherapy and prior to chemotherapy (Figure 1) revealed only a small residual nasopharyngeal volume with increased FDG uptake with a maximum SUV uptake of 4.8 compared to 11.7 pre-treatment. There was no evidence of abnormal FDG uptake in the bilateral cervical lymphatics or elsewhere. Five months after completion of external beam radiotherapy and one month after completion of systemic chemotherapy a repeat PET-CT was obtained. There was persistent soft tissue thickening in the region of the nasopharynx with evidence of abnormal FDG uptake consistent with fibrosis. An additional follow-up PET-CT was obtained 19 months after completion of radiotherapy. There was no abnormal FDG uptake in the nasopharynx or neck (Figure 1). No pathologically enlarged lymph nodes were seen in the cervical or supraclavicular regions. In the upper abdomen, two areas of abnormal FDG uptake were seen in the region of the duodenum (not shown). Endoscopy was performed which demonstrated a duodenal ulcer. Biopsy showed recurrent IDCT 20 months after completion of his initial therapy.

Salvage treatment and response

The patient's duodenal disease was treated with radiotherapy using a 3 dimensional conformal technique to deliver 54 Gy in 27 fractions. Follow-up PET-CT scan two months after salvage radiotherapy and 23 months after initial therapy to the nasopharynx primary tumor showed no active disease in any previously irradiated sites. Follow-up nasopharyngeal endoscopy demonstrated no residual lesion 23 months after treatment.

Discussion

Dendritic cells are a heterogeneous group of non-lymphoid, non-phagocytic immune accessory cells present in lymphoid and non-lymphoid organs. Several types of dendritic cells are known including follicular, interdigitating, and Langerhans' cells.¹ Each cell type provides structural and functional support of the microenvironment within lymphoid tissue. Follicular dendritic cells (FDC) belong to the accessory immune system and typically reside in lymphoid follicles. They participate in the immune response by acting as antigen presenting cells and by playing a major role in the humoral immune response.² Interdigitating dendritic cells (IDC) are antigen presenting cells characterized by interdigitating cellular junctions.³ These cells typically reside in the T-cell areas of peripheral lymphoid tissue includ-

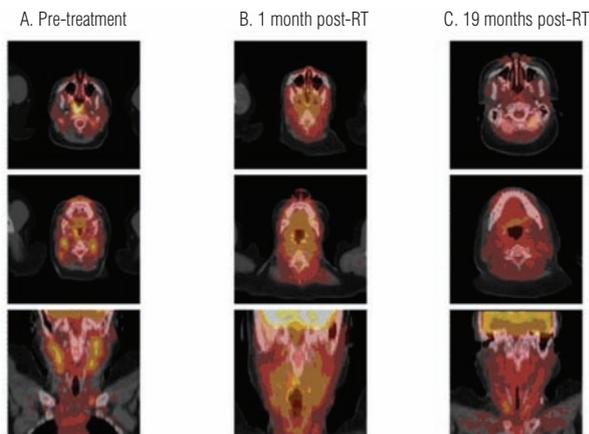


Figure 1. PET-CT imaging of pre- and post-radiation FDG uptake of the primary tumor and nodal sites.

ing Waldeyer's ring, splenic periaarteriolar lymphoid sheaths, and mucosa-associated lymphoid tissue (MALT). Langerhans' cells are also antigen presenting cells, residing in lymphoid tissue predominantly in the skin.^{4,5}

Dendritic cell neoplasms are classified by the International Lymphoma Study Group (ILSG) into four categories based on immunophenotypic groups: interdigitating dendritic cell tumors/sarcomas (IDDCT/S), follicular dendritic cell tumors/sarcomas (FDCT/S), Langerhans' cell tumors (LCT), and Langerhans' cell sarcomas (LCS).⁶ Generally, IDDCT/S is thought to be a disease entity of older individuals with a mean age at diagnosis of 71.2 years.⁷ Aggressive tumor behavior is seen in approximately one third of cases.⁷ IDDCT/S typically manifest with lymphadenopathy and have been reported in the cervical, axillary, inguinal, and regional parotid lymph nodes.^{7,8} Extranodal locations have been reported in the tonsils, nasopharynx, spleen, lung, bladder, testis, breast, and bone marrow.^{3,7-10}

FDCT/S predominantly has been documented to arise in lymph nodes^{8,11} with behavior similar to a low-grade sarcoma rather than a lymphoma.^{11,12} Nodal involvement typically presents in the cervical or axillary lymph nodes of young to middle-aged adults. Extranodal locations have been reported throughout the body, most commonly occurring in the tonsil, nasopharynx, pancreas, peripancreatic and peritoneal tissues.¹³⁻¹⁷ Extranodal locations are under-recognized most likely due to the diagnosis not being considered or recognized as demonstrated in a recent publication reviewing 46 cases suspicious for extranodal FDCT/S reported that 15 cases (33%) were misdiagnosed at the time of initial evaluation.¹⁸

Langerhans' cells, are normally present in the suprabasal squamous epithelium of the skin and mucous membranes. LCT represents a proliferation of Langerhans' cells with malignant features, typically occurring in the third to fourth decade of life. Multi-organ involvement has been reported including skin, lymph nodes, lung, bone marrow and brain, with skin

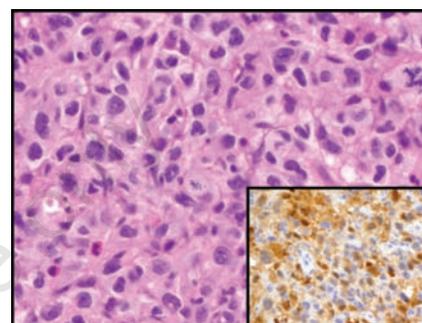


Figure 2. H&E stain of the primary nasopharyngeal tumor. The inlaid box shows diffuse CD43 positivity.

and lymph nodes being the most frequently involved organ systems.¹⁴

Generally, most dendritic neoplasms are considered low or intermediate-grade malignancies^{11,19} with the exception of IDDCT/S in which one third of cases display aggressive behavior.⁷ Various modalities have been implemented for the treatment of dendritic cell neoplasms including surgery, primary radiation therapy, systemic chemotherapy, or a combination of these modalities. No consensus has been reached as to the most appropriate treatment regimen due to the variation in reported treatment methodologies with limited published outcome data.

In patients with localized disease, the mainstay of treatment has been surgical resection with or without adjuvant treatment. Shia *et al.*¹⁸ retrospectively reviewed 46 cases of extranodal FDCT/S in which 44 of 46 patients underwent surgical resection. Local recurrence occurred in 26% of cases at a median of 15 months post resection. Forty-three percent of patients developed local and/or distant recurrence after initial treatment. Chan *et al.*¹¹ reviewed 17 cases of FDCT/S, in which 14 of 17 patients underwent surgical resection. Local recurrence occurred in 42% of patients at a median of 15 months. Six patients developed distant metastatic disease, including 4

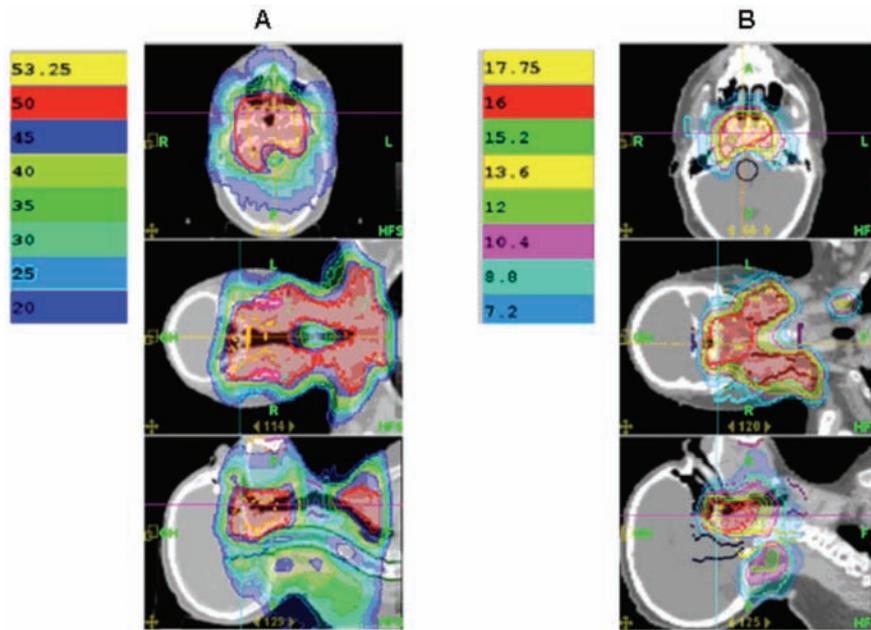


Figure 3. Representative isodose plan for treatment using image-guided IMRT.

patients who also had local recurrence.

Combined modality approaches have been sporadically reported with inconclusive benefits. Adjuvant radiation therapy has been shown to increase disease free intervals but has failed to show benefit in preventing local recurrences or distant metastasis.^{11,18} Combined treatment with radiation and chemotherapy has been utilized with limited survival benefit,^{11,18} but some studies have reported a benefit for combined radiation and chemotherapy in preventing local recurrence in incompletely excised or recurrent lesions.^{12,19}

Despite a possible benefit with radiation therapy in an adjuvant setting, the role of primary radiation is less clear. Complete and partial responses have been reported in a small number of patients. Progression free intervals ranging from five to 12 months and disease free intervals up to 4.5 years have been reported.^{7,11} Typical radiation doses that have been reported range from 50 Gy to 60 Gy.^{7,11,17} In our patient, the nasopharyngeal tumor as well as the retropharyngeal lymph nodes and bilateral involved cervical nodes were treated to 66 Gy, resulting in a complete clinical response in the primary tumor based on MRI and PET-CT 23 months after treatment. The duodenal lesion was treated with 54 Gy, achieving a complete clinical response by both PET-CT and on endoscopic evaluation three months after treatment. Dendritic cell tumors of the head and neck region are well documented in the literature with a paucity of cases reported arising in the nasopharynx. Biddle *et al.*²⁰ reviewed extra-nodal FDCS of the head and neck, in which 3 of 19 cases were located in the nasopharynx. In

all cases, surgery was implemented as the primary treatment modality. Radiation was used in an adjuvant setting in 8 of the reported cases in the setting of residual tumor after surgery. Disease free intervals in patients treated with a multimodality approach ranged from ten months to 4.5 years. IDDC/S of the head and neck region are an even rarer entity. Gaertner *et al.*⁷ reviewed 29 cases of IDDCS reported in the literature and identified 5 tumors located in the head and neck region (3 lymph nodes, one tonsil, one nasopharynx). Therapy generally consisted of surgery followed by multi-agent chemotherapy. Radiation therapy alone or in the adjuvant setting was used in several cases. In the cohort of patients, 9 died within one year of diagnosis and 7 patients were alive with stable or progressive disease at the end of treatment. With a limited number of cases, non-uniformity in treatment regimens and short follow-up, there is no standard recommendation for treatment.

Conclusions

Dendritic cell tumors of the head and neck are rare tumors, especially if they arise in extra-nodal locations. IDDC/S represents a variant with more aggressive behavior and a predilection for widespread disease. Multimodality treatment likely has some benefit in improving disease free survival and progression free survival. The role of primary radiation in the management of this disease entity remains to be determined. Our patient represents one of the few reported cases of IDDC/S

of the nasopharynx with lymph node involvement who had a complete clinical response with demonstrated local control at 23 months following primary radiation therapy. IDDC/S is a radiosensitive disease entity and high-dose radiation therapy appears to be a reasonable treatment option for patients with unresectable disease.

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