Hodgkin Lymphoma of the Nasopharynx: Case Report with Review of the Literature

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Received: 2 January 2015 / Accepted: 28 January 2015 / Published online: 3 February 2015
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Abstract We report an uncommon case and histopathologic work-up of Hodgkin lymphoma of the nasopharynx in a 49-year old female patient who presented with a 2-year complaint of bilateral nasal congestion. Histologic study revealed a lymphocyte rich subtype of classic Hodgkin lymphoma. Immunohistochemical analysis revealed CD15, CD30, OCT-2, BOB.1, and MUM-1 expression by the neoplastic cells and a lack of expression of CD45, CD20, CD3, EMA, and EBER. The review of the literature showed that Hodgkin lymphoma of the nasopharynx is rare, the most common reported subtype is the mixed cellularity, and Hodgkin lymphoma of the nasopharynx has a favorable prognosis.

Keywords Hodgkin lymphoma · Nasopharyngeal tumor · Nasopharynx

Introduction

Lymphomas are the second most common malignant neoplasms after squamous cell carcinoma in the head and neck region. Hodgkin lymphoma constitutes approximately 4 % of all lymphoma cases in the head and neck, with most of

these cases arising from a lymph node [1]. Extranodal Hodgkin lymphoma in the head and neck region is rare, with most cases involving the Waldeyer ring which is comprised of the lymphoid tissues of the base of tongue, faucial tonsils, oropharynx, and nasopharynx. These lymphoid tissues are considered extranodal but not extralymphatic.

Hodgkin lymphoma of the nasopharynx is very rare with studies putting the frequency of occurrence <1 % of total cases of Hodgkin lymphoma [2, 3]. Most reported cases have been staged IE or IIEA, and after appropriate therapy displayed very good outcomes [2, 4].

In this article, we report a case and histopathologic workup of Hodgkin lymphoma of the nasopharynx in a female patient who presented with a 2-year complaint of bilateral nasal congestion. We reviewed the literature to look at the frequency of occurrence of Hodgkin lymphoma in the nasopharynx, focusing on primary/isolated cases, the most common subtype, and therapy paradigm in reported cases.

Case Report

A 49-year-old woman presented to her primary care physician with a 2-year complaint of bilateral nasal congestion. The nasal congestion was constant. She also reported post nasal drainage which was constant and present year round. She denied any history of headaches, facial pressures or rhinorrhea. Symptoms did not respond to allergy medications, antibiotics, or steroids. A physical examination revealed no evidence of cervical lymphadenopathy or other masses.

A non-contrast computed tomography scan of the paranasal sinuses confirmed a nasopharyngeal mass with no evidence of bony erosion (Fig. 1). She was referred to

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an otolaryngologist. A diagnostic nasal endoscopic examination was performed demonstrating a large nasopharyngeal mass, occupying roughly 90 % of the nasopharynx with near complete nasopharyngeal airway obstruction. The surface of the lesion was inflamed with a central necrotic area. The lesion was biopsied and part of the specimen was sent for intraoperative frozen section consultation.

The pathologist (AGM) believed the mass represented a lymphoid neoplasm, the specifics of which would be determined on permanent section with flow cytometry and immunohistochemical analysis. Flow cytometry detected no clonal B cell or atypical T-cell population. Permanent histologic sections showed fragments of mucosal tissue consistent with sinonasal origin with prominent small lymphocytes and other inflammatory cells admixed with scattered large atypical mononucleated, binucleated, and multinucleated cells, many which were characteristic of Reed-Sternberg (R-S) cells and Hodgkin cells (R-S variants) (Fig. 2).

The lymphoid cells were negative for AE1/AE3, S100, and HMB-45 performed to evaluate for carcinoma and melanoma. The small lymphocytes were positive for CD45, CD20 (staining B lymphocytes), CD3 (staining background T lymphocytes forming rosettes around large atypical cells), and PAX5 (staining B lymphocytes). The large atypical cells were negative for CD45, CD20, and CD3. However, the cells were weakly positive for PAX5, and strongly positive for CD15, and CD30 in a typical membrane and paranuclear dot-like staining pattern. The large atypical cells were also positive for OCT-2 and MUM-1, and weak to negative for BOB.1. The small

lymphocytes and large atypical cells were negative for EMA and EBV-ISH (EBER) (Fig. 3). These findings were best classified as classical Hodgkin lymphoma. The background small lymphocytes favored a lymphocyte-rich subtype.

Due to the unusual location for a Hodgkin lymphoma and a history of non-palpable neck masses or cervical lymphadenopathy on physical examination, the case was sent for consultation and reviewed by two hematopathologist who agreed with the diagnosis. Subsequent additional clinical work-up included a full body 18-fluorodeoxyglucose positron emission tomography-CT (PET-CT) scan and complete blood count. The PET-CT scan demonstrated fluorodeoxyglucose avidity in the nasopharynx and a right level IIA lymph node measuring 2.5×1.8 cm had a maximum standard value uptake of 7.3 (Fig. 4). No evidence of lymphoma was seen in any other part of the body. The complete blood count was within reference range. She was therefore staged IIEA. The patient was referred to medical oncology based on current therapy paradigm for induction chemotherapy and radiation.

Discussion

Hodgkin lymphoma (HL) of the nasopharynx is rare, the frequency of occurrence <1 % with slightly over 100 cases reported in worldwide literature, 35 of them primarily isolated to nasopharynx without nodal involvement at presentation (Table 1) [2, 3, 5–27]. Todd and Michaels were able to identify only 38 cases including their own cases of HL involving the nasopharynx prior to 1974 in a worldwide review of the literature with just 23 cases involving the nasopharynx and neck nodes of which only 10 were considered primary/isolated [3]. These patients were not evaluated further to rule out the possibility of an occult neck lymph node involvement which could not be identified on physical examination, given that 5 of the 10 primary/isolated cases later presented with cervical lymph node involvement, and biopsy specimens were not worked up with immunohistochemical stains given the available technology at that time.

Only 6 cases were identified in the AFIP files from 1969 to 1990, out of which 4 cases were primary/isolated [17]. In 1982, Eavey and Goodman identified 2 cases of nasopharyngeal HL in a study of 500 cases of HL localized in the head and neck; both cases were stage IIA with nodal involvement [28]. In another study by Anselmo et al. [2] only 7 patients out of 2150 (0.32 %) who were diagnosed with HL from 1977 to 2001, had HL of the nasopharynx, and only a single case was primary/isolated. A more recent study by Iyengar et al. [23] identified only 9 cases of HL of

Fig. 1 A non-contrast computed tomography scan of the paranasal sinuses shows a mass in the nasopharynx

Fig. 2 Mass revealed Hodgkin lymphoma, lymphocyte rich subtype (H&E $\times 500$). *Black arrows* point to Reed-Sternberg Cells and *brown arrow* points to a large mononucleated Hodgkin cell

the nasopharynx from 1967 to 2007, from the database of M. D. Anderson Cancer Center.

Given that 9,190 new HL cases were expected to be diagnosed in 2014, and 172,937 patients are estimated to be living with the disease or are in remission in the United States [29]. HL involving the nasopharynx can be deemed to be very rare. Epstein–Barr virus (EBV) has been implicated in the etiology of HL. It is therefore of interest to understand why the nasopharynx is not a major site for HL given that it is a region known to harbor EBV. Many cases of HL of the nasopharynx have been found to be negative for EBV including our reported case [17, 22, 24].

In our review of the literature the commonest subtype of HL of the nasopharynx was the mixed cellularity which is in concordance with other reported literature [4, 17, 20]. Contradicting this is a study by Quinones-Avila et al. [22] who found that lymphocyte rich HL (4 of 10) was most common: they suggested that this may be attributed to the fact that the lymphocyte-rich subtype of classical HL was not recognized until 1994 when it was proposed by Revised European-American Lymphoma classification.

Head and neck pathologists should be wary about making a diagnosis of HL in extranodal head and neck site due to its rarity and because other lymphoma entities in the differential diagnosis are more common in this anatomic site. However, these cases definitely do exist. The

following differential diagnosis should be considered: T-cell lymphomas, T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), EBV+ diffuse large B-cell lymphoma of the elderly (EBV + DLBCL), infectious mononucleosis (IM), and B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (grey zone lymphoma).

Non-Hodgkin T-cell lymphomas are relative common in the sinonasal region but they can be differentiated from HL based on atypical T-cell population which can usually be detected on flow cytometry and by immunohistochemical stains. THRLBCL can be differentiated from classical HL by the presence of CD20 positive large B-cells, which are CD15 and CD30 negative, and from nodular lymphocyte predominant HL by the absence of small B-cells, and presence of CD57 negative, CD8, and TIA1 positive T-cells [30, 31]. EBV + DLBCL can be differentiated from classical HL by the presence of CD20 positive large B-cells, which are variably CD30 positive but CD15 negative, and from nodular lymphocyte predominant HL by the absence of nodular morphological architecture and absence of numerous background T-cells. IM can be differentiated from HL by the presence of activated lymphocytes (Reed-Sternberg like cells), which are LCA/CD45, CD20 or CD3 positive, and may express CD30 but lack

Fig. 3 Immunohistochemical panel **a** cytokeratin negative, **b** S100 negative, **c** HMB45 negative, **d** CD45 positive in small lymphoid cells but negative in large atypical cells, **e** CD20 positive in some small lymphoid cells but negative in large atypical cells, **f** CD3 positive in numerous small lymphoid cells forming rosettes around negative large atypical cells, **g** PAX5 weakly positive in large atypical cells, **h** CD15 positive in a typical membrane and paranuclear dot-like staining pattern in large atypical cells, **i** CD30 positive in a typical membrane and paranuclear dot-like staining pattern in large atypical cells, **j** MUM-1 positive in large atypical cells, **k** OCT-2 positive in large atypical cells, **l** BOB.1 weak to negative in some large atypical cells, **m** epithelial membrane antigen negative in small lymphoid and large atypical cells, and **n** EBER negative in small lymphoid and large atypical cells (original magnification $\times 1,000$)

CD15 expression. Grey zone lymphoma can be differentiated from classical HL by the presence of uniform strong expression of CD20 and other B-cell markers (PAX5, CD79a) and absence of CD15 [30].

The case being reported upon is a lymphocyte-rich classic Hodgkin lymphoma (LRCHL), which also needs to be differentiated from a nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Morphologically,

LRCHL may demonstrate a common nodular pattern similar to NLPHL and the Hodgkin and Reed-Sternberg (HRS) cells in LRCHL may also resemble the popcorn or lymphocyte predominant (LP) cells in NLPHL. However, HRS cells are CD45 negative, CD20 negative but not always as 25–40 % of classic Hodgkin lymphoma may express CD20 with variable intensity [31, 32], PAX5 positive in a weak to moderate intensity, MUM-1 positive in most cases, OCT-2 and BOB.1 can be both positive in LRCHL [33], and expression of both CD30 and CD15. While LP cells are CD45, CD20, and PAX5 positive in a strong intensity, OCT-2 and BOB.1 are also positive. MUM-1 and CD30 are negative; however, weakly positive in rare cases and CD15 negative [34]. Therefore, the use of immunohistochemical stains in the confirmation of primary diagnostic entities in the nasopharynx is essential.

The trend in management of these patients seems to have changed from radiation alone to a combination therapy of two or more cycles of chemotherapy (ABVD regimen: Adriamycin, bleomycine, vinblastine, and dacarbazine) and

Fig. 4 PET-CT scan. Arrows point to areas of fluorodeoxyglucose avidity in the nasopharynx and right level IIA lymph node

Table 1 Case reports of primary/isolated Hodgkin lymphoma of the nasopharynx in the literature

	References	Age	Sex	Treatment	Other site involved at diagnosis/subtype
1	Sobol [5]	52	F	Surgery and RT	None
2	Bauer [6]	41	F	Surgery, RT, CT	None
3	Manci [7]	15	M	RT	None
4	Ghossein [8]	42	M	RT	None
5	Leonardelli [9]	30	M	RT	None
6	Leonardelli [9]	65	M	RT	None
7	Trentini [10]	49	F	RT	None
8	Bogusz [11]	7	M	RT	None
9	Todd [3]	32	F	RT	None/MC
10	Todd [3]	24	M	RT	None/LP
11	O'Riley [12]	62	M	RT	None/LP
12	Daniel [13]	23	M	Surgery and RT	None/MC
13	Strutz [14]	27	M	Surgery and RT	None/LP
14	Strutz [14]	46	F	Surgery and RT	None/LP
15	Krzeska-Malinawska [15]	35	F		
16	MacNaughton [16]	11	M	Surgery and CT	None/LP
17	Kapadia [17]	47	M	RT	None/MC
18	Kapadia [17]	74	F	RT	None/NS cellular phase
19	Kapadia [17]	64	F	RT	None/MC
20	Kapadia [17]	54	F	RT	None/interfollicular
21	Kapadia [17]	36	F	RT	None/interfollicular
22	Malis [18]	52	M	RT	None/NS
23	Herrmann [19]	43	F	Surgery	None/NS
24	Anselmo [2]	34	M		None/LP
25	Abbes [20]	41	M	RT	None/MC
26	Takashima [21]	46	M	CT	None/classical Hodgkin
27	Quinones-Avila [22] and Iyengar [23]	47	F	CT and RT	None/LR
28	Quinones-Avila [22] and Iyengar [23]	53	M	CT and RT	None/LR
29	Quinones-Avila [22] and Iyengar [23]	24	M	CT and RT	None/LD
30	Quinones-Avila [22] and Iyengar [23]	57	M	CT and RT	None/LR
31	Kochbati [24]	41	M	RT	None/MC
32	Atasoy [25]	45	F	RT	None/MC
33	Iyengar [23]	6	M	RT	None/MC
34	Johnson [26]	50	F	CT and RT	None/LR
35	Ocalan [27]	53	M	CT and RT	None/NS

RT radiotherapy, CT chemotherapy, MC mixed cellularity, LP lymphocyte predominance, NS nodular sclerosis, LR lymphocyte rich, LD lymphocyte depleted

radiotherapy of the nasopharynx and cervical lymph nodes at a dosage ranging 20–50 Gy in fractions [2, 23, 26]. Most patients are staged I or II, and have a good prognosis, including continuous complete remission in patients with localized disease (stage I or II) [2, 23].

In conclusion HL of the nasopharynx is rare, but should be included as a possible differential diagnosis when a patient presents with a nasopharyngeal mass, and proper investigative and immunohistochemical stains should be performed to rule out other lymphoid neoplasms.

Acknowledgments We would like to acknowledge Drs. Raymond Felgar and Fiona Craig for reviewing the slides of this case.

Conflict of interest All authors declare that there are no financial conflicts associated with this report and that the funding source has no role in conceiving and performing the study.

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