B Lymphoblastic Lymphoma Presenting as a Tumor of the Nasopharynx in an Adult Patient

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Abstract In adults, non-Hodgkin's lymphoma (NHL) is the second most common neoplasm found in the head and neck region after squamous cell carcinoma. Within this region, primary NHL of the nasopharynx is rare. We report the case of a 28-year-old male diagnosed with a B lymphoblastic lymphoma (CD20–; CD79a+; CD3–; CD10+; PAX5+, CyclinD1–; TdT+) of the nasopharynx extending to the deep and superficial structures of the right hemiface, to the skull base with an intracranial component and a small but detectable bone marrow involvement, who was started on chemotherapy with a complete response. To the best of our knowledge, this is the first case of a primary nasopharynx B-LBL in an adult patient with such aggressive regional spread to be reported in the literature.

Keywords Non-Hodgkin lymphoma · B lymphoblastic lymphoma · Head and neck · Waldeyer's ring · Nasopharynx · Chemotherapy

Introduction

NHL is a group of histologically and biologically heterogeneous clonal malignant diseases arising from the lymphoid system. B-cell type NHL comprises about 85%, the remaining being of T cell-type or NK cell-type [1]. Primary extranodal site is the form of presentation of approximately 25–40% of all NHL [2]. After the gastrointestinal tract, extranodal NHL arising in the head and neck (the Waldeyer's ring tonsils being the commonest affected site) follows, accounting for 10% of all NHL and 1% of head and neck tumours [3]. Primary NHL of the nasopharynx corresponds to a small proportion of Waldeyer's lymphomas [4] with an aggressive clinical course and poor outcome even in the early stages [4, 5].

B lymphoblastic lymphoma (B-LBL) is an uncommon form of high grade aggressive lymphoma accounting for less than 10% of the total cases of lymphoblastic lymphoma and 0.3% of NHL in adults, with a male predominance [6, 7]. Frequent sites of involvement of B-LBL include the skin, soft tissue, bone and lymph nodes [8].

We report the case of a 28 year-old-man diagnosed with a primary nasopharynx B-LBL and discuss some aspects of NHL in this anatomic area including therapeutic options. We also review the published cases of primary B-LBL in the head and neck region.

Case Report

A 28-year-old previously healthy male Caucasian patient presented with progressive worsening of chronic sinusitis with nasal obstruction, mucopurulent rhinorrhea and frontotemporal headache of 6 months duration. Three months before his hospital admission, he had complained of right

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Fig. 1 Cranial, orbit and maxillo-facial MRI. **a–c** (axial sections, T2 weighted images), **d** (coronal section, T1 weighted images), **e,f** (axial sections, after gadolinium). Bulky neoplastic expansive lesion with epicentre in the right nasopharynx, multivectorial spread to the retropharyngeal space of the right oropharynx, right carotid space, pterygomaxilar fossa, infra-zygomatic space, and pterygoid muscles;

obliteration of the arial space of the nasopharynx; invasion of the right ethmoidal cells, right maxilar sinus and partial invasion the sphenoidal sinus; infiltration of the posterior-inferior side of the right orbit with proptosis of the eye; invasion of the skull base with involvement of the cavernous sinus and probable peri-neural infiltration of the trigeminus nerve

otalgia, with tinnitus and hearing impairment, hypoesthesia of the right hemiface, and had more recently noticed a right infraorbital swelling causing exophthalmos of the homolateral eye with ensuing diplopia. No fever, pruritus, night sweat or weight loss were noted. On clinical examination, facial asymmetry was pronounced with a palpable infraorbital and nasal mass on the right hemiface and homolateral exophthalmos. Full otorhinolaryngologic examination showed right otitis, edema of medium and low

turbinate with complete blockade of right nasal fossa and edema with bulging of the posterior half of the hard palate. No palpable lymph nodes or organomegaly were present.

Cranial, orbit and maxillo-facial MRI scan showed a bulky expansive lesion whose epicenter was in the right nasopharynx and involving the homolateral nasal hemifossa, maxilar sinus and ethmoidal cells, sphenoidal sinus, pterygopalatine fossa and postero-inferior region of right orbit with intracranial extension. The orbital component

Fig. 2 Nasopharyngeal cavum biopsy specimen histology. Diffuse proliferation of small monomorphic lymphoid cells with scanty cytoplasm, small round and irregular nuclei, condensed nuclear chromatin and indistinct nucleoli without epithelial permeation and numerous mitotic figures with focal “starry sky” pattern: Hematoxylin-eosin stain (×400)

determined proptosis of the ocular globe and enlargement of optic canal. Moreover, it showed probable involvement of the trigeminus nerve (Fig. 1a–f). Blood count and biochemical tests were all normal. Biopsy of the nasopharynx cavum lesion guided by nasopharyngeal endoscopy showed a neoplasm histologically with a dense, diffuse proliferation of small monomorphic cells with scanty cytoplasm, small round and irregular nuclei, condensed nuclear chromatin and indistinct nucleoli without epithelial permeation and numerous mitotic figures with focal “starry sky” pattern (Fig. 2). Immunohistochemical analysis (CD20–; CD79a+; CD3–; CD10+; PAX5+, CyclinD1–; TdT+) was compatible with a B-LBL (Fig. 3a, b). Further staging investigations showed no lymph node or other organ involvement, except minimal bone marrow infiltration by a

small subpopulation of pathological cells with an immunophenotype (CD19+; CD45+; cytoplasmatic CD79a+; CD34+; CD20–; CD10+; anti-bcl2+; CD5–; TdT+; and no expression of light chains) concordant with the biopsed lesion, thus confirming the diagnosis.

BCR-ABL1 fusion gene was not detected by fluorescent in situ hybridization in the biopsed specimen.

The patient was scheduled for chemotherapy according to hyper-CVAD regimen [9].

CSF was normal, showing no malignant cells. After 4 of a total of 8 cycles, a complete imagiological resolution of the lesion was observed. The patient is now under maintenance therapy (with daily mercaptopurine, weekly methotrexate, monthly vincristine, prednisolone and trimestral administration of intratecal chemotherapy), and in complete remission of the disease after 2 years.

Discussion

NHL of the head and neck comprises a diverse group of distinct clinicopathologic entities. Although representing the second most common neoplasm found in the head and neck region in the adult population, it is very uncommon, constituting only 1% of head and neck cancers, the majority of them being squamous cell carcinomas or one of their variants [10, 11]. A high degree of suspicion is required to avoid unnecessary radiologic and surgical procedures since NHL can be mistakenly diagnosed as carcinoma. Virtually any site in the extracranial head and neck can be affected by NHL and three distinct categories of involvement can occur. Nodal NHL is the most common, followed by extranodal lymphatic (Waldeyer's lymphatic ring) and extranodal extralymphatic sites (orbit, sinus, nose, mandible, deep facial spaces, parotid gland, and dermis) [12]. In the case reported here, the patient's MRI scan pointed to a primary lesion originary of the extranodal lymphatic Waldeyer ring (nasopharynx) with multivectorial spread to other extranodal extralymphatic

Fig. 3 Nasopharyngeal cavum biopsy specimen immunohistochemical profile. These cells are positive for TdT (a, ×400) and positive for PAX5 (b, ×400), compatible with the diagnosis of B lymphoblastic lymphoma

Table 1 Summary of clinical data, cytogenetic study, treatment and response of the reported cases of primary head and neck B lymphoblastic lymphoma of adults

Author	Age (years)	Sex	Primary localization	Stage	Cytogenetics	Treatment	Response	Follow-up (months)
Our case	28	M	Nasopharynx	IV	Normal	CT(hCVAD)	CR	26
Nishihara [25]	48	M	Neck (cervical spinal)	I	NA	CT(hCVAD) +RT	CR	NA
Cox [24]	46	F	Oral cavity (mandible)	I	NA	CT(CHOP +MTX)	CR	‡
Kajimoto [22]	16	F	Orbit	I	NA	CT(hCVAD) +RT	CR	NA
Shinkuma [19]	64	F	Orbit (eye bulb)	I	NA	CT(CHOP)	CR	8
Aakalu [23]	21	M	Orbit	I	NA	CT	CR	NA
Kim [20]	65	M	Skin (head and neck)	I	NA	CT	CR	NA
Lin [7]								
Case 1	27	M	Skin (scalp)	I	NA	CT(hCVAD)	CR	12
Case 2	62	M	Skin (scalp)	II	NA	NA	NA	NA
Case 3	20	M	Conjunctiva, parotid	I	NA	NA	NA	NA
Schafer [21]								
Case 1	66	M	Skin (scalp)	I	MLL (11q23)	CT (ALL-type)	CR	‡
Case 2	27	M	Skin (scalp)	I	Hyper diploid to triploid	CT (ALL-type)	CR	34

M Male, F female, NA not available, CT chemotherapy, RT radiotherapy, CR complete response, ‡ deceased

Table 2 Summary of immunophenotyping profile of the reported cases of primary head and neck B lymphoblastic lymphoma of adults

Author	Tdt	CD3	CD5	CD10	CD19	CD20	CD79a	CD34	CD45	PAX5	CiclinD1	sIg
Our case	+	—	—	+	+	—	+	+	+	+	—	—
Nishihara [25]	+	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA
Cox [24]	+	—	NA	NA	NA	+	NA	—	NA	NA	NA	NA
Kajimoto [22]	+	NA	NA	+	NA	NA	+	NA	NA	NA	NA	NA
Shinkuma [19]	+	NA	+	+	+	+	NA	NA	NA	NA	—	NA
Aakalu [23]	+	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA
Kim [20]	+	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA
Lin [7]												
Case 1	+	—	NA	+	+	—	+	NA	+	NA	NA	—
Case 2	+	—	NA	+	+	+	NA	NA	+	NA	NA	—
Case 3	+	—	NA	—	NA	+	+	+	+	NA	NA	—
Schafer [21]												
Case 1	+	NA	NA	—	+	—	NA	—	NA	NA	NA	NA
Case 2	+	NA	NA	+	NA	+	NA	+	NA	NA	NA	NA

+ Positive, —negative, NA not available or not done

regions most notably the orbit, right maxilar sinus, right ethmoidal sinus, sphenoidal sinus and even an intracranial component with possible invasion of the trigeminus nerve. Primary nasopharyngeal NHL is infrequent in adults, representing a small fraction (10–28%) of Waldeyer's ring lymphomas [4], with a higher incidence in males in the sixth decade of life [13]. According to the literature the largest proportion of Waldeyer's lymphoma are of B cell origin with diffuse large B cell lymphoma being the

commonest histological variant [14, 15] while T cell-type lymphoma is more common in the nasopharynx and nasal cavity [16, 17]. Nasopharyngeal NHLs like other Waldeyer's ring lymphomas tend to be a localized disease, the majority (60–90%) of patients presenting an intermediate to high grade disease in an early stage (stages I and II) [4, 13]. Contrary to the common findings, our patient had a primary nasopharyngeal NHL of precursor B cell origin (B-LBL) and not mature B cell as in B diffuse large B cell

lymphoma, without nodal involvement, locoregionally aggressive with stage IV disease (bone marrow involvement, although minimal).

B lymphoblastic lymphoma (B-LBL)/leukemia (B-ALL) are originated from B cell lineage. B-LBL/B-ALL represent different clinical presentations of the same neoplasm, being histologically and immunophenotypically identical. When the process is confined to a mass lesion with or without minimal evidence of blood and marrow involvement, the diagnosis is lymphoma, but when extensive marrow and blood are involved, lymphoblastic leukemia is the appropriate term [1]. B-LBL is a rare subtype of NHL seen primarily in children [18]. As far as we know there are no reports of primary nasopharyngeal localization of B-LBL in adults with head and neck NHL, and published cases of head and neck B-LBL in adults are very scarce. A review of the available cases in the literature of head and neck primary B-LBL in adults including our case, with clinical, immunophenotyping, cytogenetics and therapeutics, is summarized in Tables 1 and 2 [7, 19–25].

NHL are usually treated with radiotherapy in low grade stage I and II disease, however combined modality treatment including chemotherapy and radiotherapy is advocated in localized, intermediate to high grade aggressive forms of the disease. For advanced disseminate disease and high grade histology, aggressive chemotherapy with or without radiotherapy is recommended. The CHOP regimen (cyclophosphamide, hydroxydaunomycin, oncovin/vincristine, and prednisone) plus Rituximab (if CD20 positive in immunochemistry) is considered as the standard combined chemotherapeutic treatment [26–28]. Due to the biologic unity and the aggressiveness of B-LBL/B-ALL, intensive therapy is required. CHOP regimen is an insufficient therapy for B-LBL [29], so the treatment approach used in this case was based on the hyper-CVAD regimen, an acute lymphoblastic leukemia-type combination of multidrug chemotherapy with high-dose methotrexate and cyclophosphamide which has proven to be a much more effective regimen [9, 30, 31].

Patients with B-LBL treated with aggressive chemotherapy have higher complete remission rate and remission duration than reported for adult patients with B-ALL treated with similar regimens, suggesting that B-LBL behaves biologically like a low-risk or the favorable subset of intermediate-risk B-ALL [7, 8].

Adverse prognostic factors in B-ALL includes very young age (<1 year), increasing age (>10 years), presence of central nervous disease, high white blood cell count, cytogenetic abnormalities, slow response to initial therapy, and presence of minimal residual disease after therapy. Prognostic factors in B-LBL are essentially unknown owing to the rarity of the disease and the few previous attempts to separate this subgroup from the B-ALL.

Apparently, the survival advantage of patients with B-LBL is due to the disease being frequently localized with low tumor burden and with low propensity for peripheral blood and marrow involvement [7, 32]. Our patient had a high tumor burden (bulky nasopharyngeal with extensive local spread and detectable marrow infiltration), but responded very well to the treatment, having been in complete remission for more than 2 years. This factor alone could be the paramount prognostic factor regardless of the initial disease features. Moreover, the absence of cytogenetic abnormalities contributed to the good outcome of this case.

In summary, we report this case of a patient with a high grade advanced stage aggressive primary nasopharyngeal NHL of B-LBL subtype which was successfully managed by aggressive chemotherapy. Bearing in mind that B-LBL constitutes less than 0.3% of all NHL and that primary extranodal NHL represents less than 1% of total head and neck tumors, its presentation in such an uncommon place as the nasopharynx constitutes a unique finding and emphasizes the importance of early recognition and diagnosis of this rare but potentially treatable disease.

Conflicts of interest The authors declare no conflicts of interest.

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