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Large B-cell lymphoma with IRF4 rearrangement: a special tonsillar lymphoma in children

Jie Man [a], Yizhen Wang [b], Xiaowen Zhai [a,*], Lian Chen [c], Yangyang Ma [c], Hongsheng Wang [a]

[a] Department of Hematology and Oncology, Children's Hospital of Fudan University, NO.399 Wanyuan Rd, Minhang District, Shanghai, 201102, China
[b] Department of Pathology, Anhui Provincial Children's Hospital, NO.39 Wangjiang East Rd, Baohe District, Hefei City, 230051, Anhui Province, China
[c] Department of Pathology, Children's Hospital of Fudan University, NO.399 Wanyuan Rd, Minhang District, Shanghai, 201102, China

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ABSTRACT

Objective: To identify the clinicopathological features and prognosis of large B-cell lymphoma(LBCL) with interferon regulation factor 4 (IRF4) rearrangement.
Methods: We retrospectively analyzed the medical records of four patients from Children's Hospital of Fudan University diagnosed with LBCL with IRF4 rearrangement during Sep. 2014 to Oct. 2018, and performed a literature review.
Results: Four patients had an average age of 5.7 years. The median duration from presentation to final diagnosis was 25.7 days. All 4 patients were admitted to the hospital due to severe snoring with no causes. The patients showed enlarged lymph nodes in the neck without tenderness. All 4 cases presented as localized disease (St-jude stage II). Lactate dehydrogenase (LDH) and serum albumin were all in the normal range. Morphology showed that normal lymphoid follicles were diffusely invaded by consistent, medium-sized large cells with obvious nucleoli. CD20, CD79α, PAX5, CD10 and BCL6 were diffusely positive. Neoplastic cells were also strongly positive for MUM1 and Ki-67. IRF4 gene rearrangement was detected as positive by IRF4 dual-color break-apart probe. Four patients underwent routine chemotherapy post bilateral tonsillectomy operation. Three achieved complete remission (CR) while the newly diagnosed one is during the second course of chemotherapy.
Conclusions: Tonsillar LBCL with IRF4 rearrangement in children presents distinct clinicopathologic and molecular genetic features, and it usually has a favorable outcome.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a common type of B-cell non-Hodgkin lymphoma(NHL) that is usually accompanied by characteristic features of immunoglobulin (Ig) gene translocation [1]. By screening for novel IgH translocation partners in cases of pediatric and adult lymphomas, Salaverria et al. [2]identified chromosomal translocations juxtaposing the IRF4 oncogene next to one of the Ig loci as a novel recurrent aberration in mature B-cell lymphoma. Currently, limited studies have reported on the clinical, histological and molecular features of this kind of LBCL which is listed as an independent lymphoma entity in the WHO classification of lymphoid neoplasms in 2016 [3]. We report on 4 cases and review related literatures to further discuss the clinicopathologic features, treatment and prognosis of the disease.

2. Patients and results

Table 1 summarizes the pertinent clinical and pathologic findings of these 4 patients, including 3 girls and 1 boy with ages of 8, 6, 2.7 and 6 respectively. All 4 patients were with the complaint of with severe snoring and open-mouth breathing during sleeping. The first patient presented with bilateral enlarged tonsils and several tough lymph nodes in the neck with a diameter of approximately 1 cm. LBCL was considered through pathological

* Corresponding author. Department of Hematology and Oncology, Children's Hospital of Fudan University, NO.399 Wanyuan Rd, Minhang Distric, Shanghai, 201102, China.
E-mail address: zhaixiaowendy@163.com (X. Zhai).
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Abbreviations

LBCL	large B cell lymphoma
IRF4	interferon regulation factor 4
DLBCL	diffuse large B cell lymphoma
LDH	lactate dehydrogenase
CR	complete remission
PFS	Progression-free survival
pFL	pediatric follicular lymphoma

Table 1
Clinicopathologic features of tonsillar lymphoma with IRF4 rearrangement.

	Case1	Case2	Case3	Case4
Sex	female	female	male	female
Age	8	6	2.7	6
Primary Site	bilateral tonsils	bilateral tonsils	left tonsil	left tonsil
St-jude Stage	II	II	II	II
CD20	+	+	+	+
CD10	+	—	—	—
MUM1	+	+	+	+
Bcl-2	+	—	—	—
Bcl-6	+	+	+	+
CD5	—	—	—	—
TdT	—	—	—	—
ki-67	70%+	90%	90%	90%
IRF4-trans	+	+	+	+
Hemoglobin(g/L)	136	130	127	138
LDH(IU/L)	178	211	288	193
Treatment	NHL-BFM-90	COPAD	COPAD	COPAD
Follow-up (months)	NED (55)	NED (15)	NED (15)	NED (8)

morphology. Staging procedures including ultrasound (US) examination, enhanced computed tomography (CT), bone marrow aspiration and cerebrospinal fluid cytology showed a St Jude stage II disease. She received 4 cycles modified NHL-BFM 90 chemotherapy regimen (dexamethasone, cyclophosphamide, vincristine, ifosfamide, methotrexate, etoposide, and cytarabine) and was in complete remission (CR) for 55 months.

The second patient presented with hypertrophy of both tonsils, and tough lymph nodes with a diameter of 1.8 cm that could be palpated in the left neck and right submandibular area. Routine blood cells and serum LDH and albumin levels were within normal ranges. A diagnosis of DLBCL was made through tonsillectomy specimen with complete resection of the tonsil.

Magnetic resonance imaging (MRI) of the nasopharynx after the bilateral tonsillectomy (Fig. 1) showed that the sidewall of the nasopharynx was slightly thickened, which suggested an inflammation response without any other special clinical significance. The patient was treated with 2 cycles of COPAD regimen. She was in complete remission for 15 months.

The third patient presented with a left tonsillar mass for about 1 month. Physical examination showed several fused lymph nodes with a diameter of approximately 2 cm in the neck. Based on the results of pathological morphology, US, CT scan, bone marrow aspiration and cerebrospinal fluid cytology, he was diagnosed as St Jude stage II LBCL. The patient has been followed up for 15 months and recovered post-surgery followed with two cycles of COPAD regimen.

The fourth patient presented with snoring and the left tonsil enlarged for 1 month. She underwent bilateral tonsillectomy and a diagnosis of IRF4-rearrangement LBCL was made. US revealed multiple hypertrophy of lymph nodes in the neck but the largest one was only 1.5 cm in diameter. ^{18}F-fluodeoxyglucose (FDG) positron emission tomography (PET)-CT showed indeterminate mass in the nasopharynx, oropharynx, laryngopharynx and the largest lymph node with an increased intake of FDG (maximum standard uptake values, 3.6, 2.6, 2.8, 2.0 respectively) (Fig. 2). Staging procedures including CT scan, PET-CT and bone marrow aspiration showed a St Jude stage II disease. The patient currently has recovered post given two cycles of COPAD chemotherapy and has been regularly followed up for 8 months.

Pathology of all 4 specimens showed that the structure of lymphoid follicle was destroyed in some areas. Part of the lymphoid follicles expanded while the interfollicular zone was compressed. Instead, sheets of moderate-to large-sized cells with vacuolated nuclei were diffusely infiltrated. Some of the nucleoli were obvious, and the nuclear division was visible (Fig. 3A, B and C). The immunohistochemistry results are listed in Table 1 and showed in Fig. 3D~I. The tumor cells of 4 cases expressed CD20 and MUM1.The proliferation index by ki-67 staining was high showing over 90% in 3 patients and 75% in one. Neoplastic cells of patient 1 were positive for CD10 and Bcl-2 while negative in the other 3 patients. All cases stained for CD5 and TdT were negative.

Fluorescence in situ hybridization (FISH) using dual-color break-apart probe for IRF4 detected the chromosomal translocation in all 4 cases (Fig. 4).

3. Discussion and literature review

IRF4/MUM1 which is a transcription factor located at the 6p25 locus of the chromosome, plays an important role in the growth and differentiation of B cells [4]. The overexpression of MUM1 is

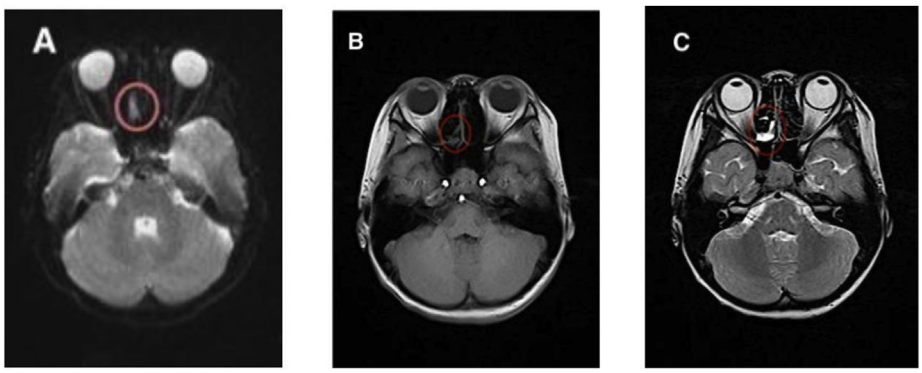

Fig. 1. Magnetic resonance imaging (MRI) of the nasopharynx after the bilateral tonsillectomy in patient 2. (A) The sidewall of the nasopharynx displayed as a soft tissue signal; (B) Equal signal in the T1 phase; (C) High signal in the T2 phase and partially enhanced after CT enhancement.

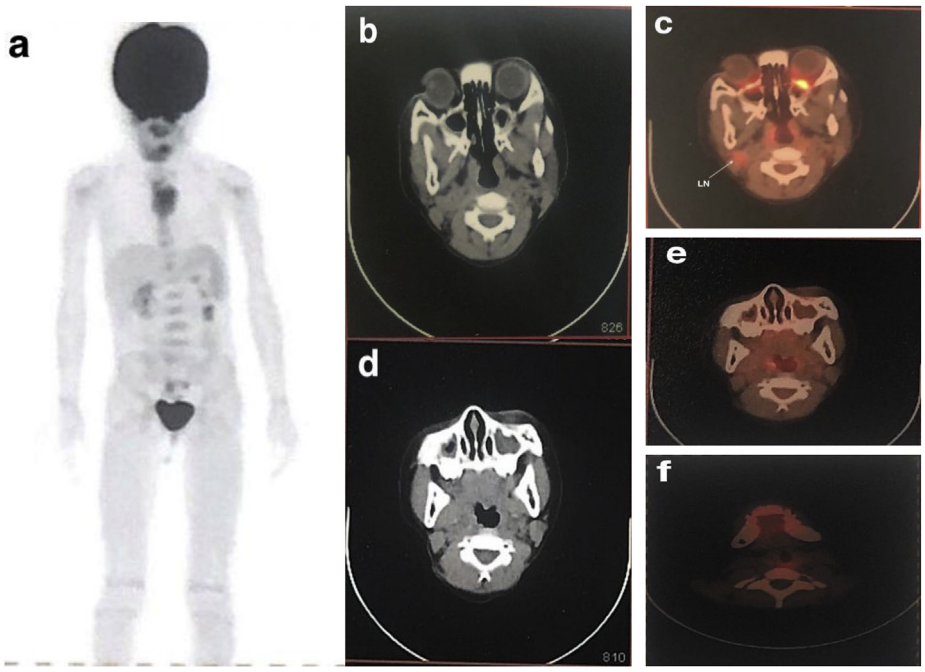

Fig. 2. PET-CT images of patient 4. MIP image shows the distribution of FDG (a). CT plain scan showed no abnormal density of the nasopharynx(b) and oropharynx(d). PET/CT showed mild radioactivity intake in nasopharynx (c; SUVmax = 3.6), oropharynx (e; SUVmax = 2.6) and laryngopharynx (f; SUVmax = 2.8) after bilateral tonsillectomy. The arrow pointed to the largest lymph node in the right neck (SUVmax = 2.0).

often activated by IRF4 rearrangement which was mainly reported in multiple myeloma [5] and was first reported in B-cell lymphoma in 2011(2).Immunohistochemical staining of MUM1 was positive in 50%–70% of LBCLs, while the incidence of IRF4 rearrangement in LBCL originating from Waldeyer's ring is only 8% [6].These data suggests that not all MUM1 expression is caused by IRF4 rearrangement, other mechanisms may exist.

Although DLBCL is the primary type of adult NHL [7], LBCLs with

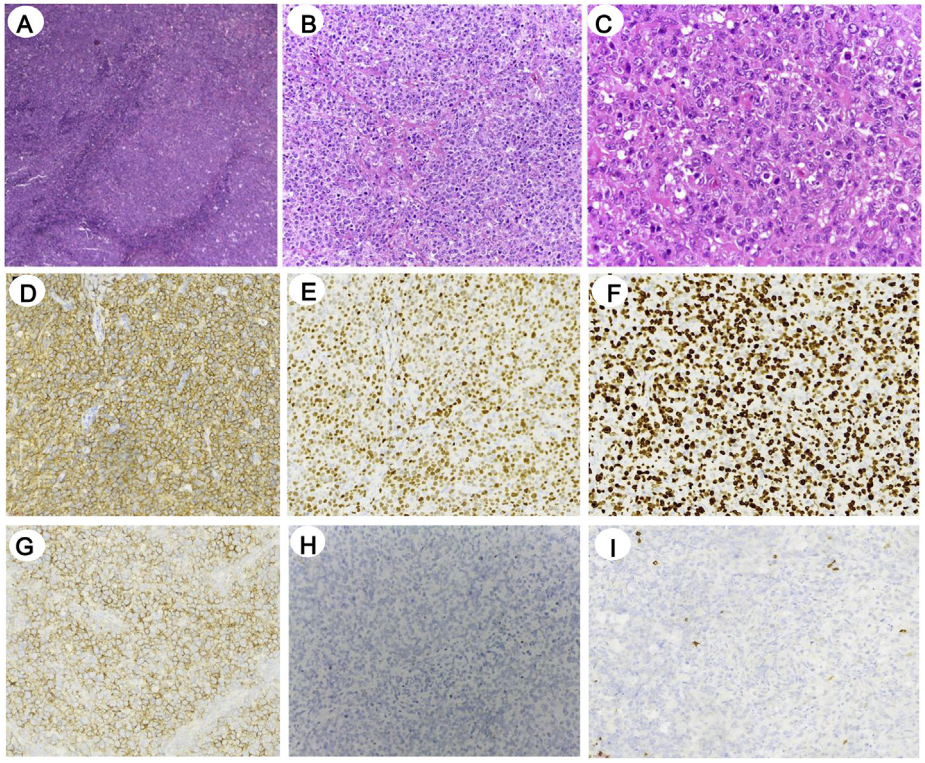

Fig. 3. Morphology and immunohistochemistry of follicular in the tonsil. The normal lymphoid follicle structure was destroyed in some areas. Part of the lymphoid follicles expanded, and the interfollicular zone was compressed (A, HE, X40). The tumor is composed mainly of large to intermediate neoplastic cells with vacuolated nuclei (B, HE, X200). Some neoplastic cells show obvious nucleoli, and nuclear division was visible (C, HE, X400). Neoplastic cells showed positivity for CD20, MUM1, ki-67(D, E, F respectively, HRP, X200) but negatively for CD5(I, HRP, X200). The immunohistochemistry results of CD10 showed positive in patient 1(G, HRP, X200) but negative in patient 2(H, HRP, X200).

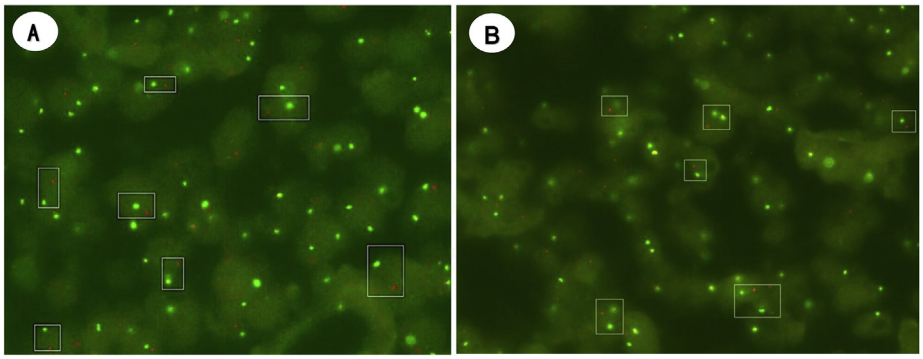

Fig. 4. FISH for IRF4 dual-color break-apart probe. Split red/green signals surrounded by the white rectangle in tumor nuclei indicate IRF4 rearrangement (A, patient 2; B, patient 3).

IRF4 rearrangement are more likely to be diagnosed in children and adolescents. This type of lymphoma is usually located in Waldeyer's ring, which represents the most common extranodal site for B-cell lymphoma [[8]], and tonsils account for 70% of this area. Malignant tonsillar lymphomas occurring in the elderly also express MUM1, but there were no reports of IRF4 rearrangement detected. In adults, three IRF4-rearrangement LBCLs originating from lymph nodes were reported in Japan in 2013 [9], and then one case of inguinal lymph node origin reported in India in 2018 [10]. Pediatric lymphomas of the tonsils are especially rare. Only four cases have been diagnosed at our hospital, and coincidently they were all accompanied by IRF4 rearrangement. These features of presenting at early [11]onset age (all <8 years old), primarily in the tonsils, St Jude stage II and normal LDH levels and confined to the primary site or to the regional lymph nodes may cooperate to restrict the invasive growth pattern of neoplastic cells. Clinically, the patients showed no systemic manifestation except snoring with rapidly enlarging tonsils. In addition, lymphadenopathy is commonly present in tonsil malignancy, but it was easily neglected because of no related clinical symptoms. In fact, we consider it an infective rather than lymphomatous involvement. Partly because the diameters of the largest one of four patients are all lower than 2 cm, on the other hand, the maximum SUV of patient 4 is lower than 2.5 and no obvious corresponding mass was presented on CT scan image. These findings suggest that clinical concern for malignancy should include rapidly enlarging tonsils but asymmetry with local lymphadenopathy as described in a systematic review [12].

Pathological morphology showed that normal lymphoid follicles were instead of large, expansive follicles comprising predominantly centroblasts or moderate-to large-sized blastoid cells. Neoplastic cells with round nuclei and scant cytoplasm display a diffuse infiltration pattern and grow to form a large lymphoid follicular structure. The special pattern restricted the invasive growth of lymphoma cells and are more consistent with pediatric follicular lymphoma (pFL) as described [13]. IRF4 rearrangement can activate IRF4 gene transcription and consequently cause the overexpression of MUM1 [14]. One case was positive for the germinal center (GC) markers, including CD10 and BCL2, but the other three cases were negative. According to Hans algorithm, DLBCL was subdivided into Germinal Centre B (GCB) and non-GCB subtypes based on immunohistochemistry results [15]. Expression of CD10 is an indicator of GCB cell origin. This finding suggested that LBCLs with IRF4 rearrangement comprise heterogeneous histopathological subtypes originating from different cells like DLBCL, which may be the point of differential diagnosis with the pFL with the GC cell origin.

As a kind of B-cell lymphoma, LBCLs with IRF4 rearrangement have been reported sensitive to chemotherapy in previous studies. The cure rate of combined chemotherapy after tonsillectomy is almost 100%. Four patients in this study all received surgical excision followed by chemotherapy and achieved CR. One patient underwent a 4-cycle modified NHL-BFM-90 regimen and has attained PFS for over 4 years. Three patients achieved CR after finishing a 2-cycle COPAD regimen and were followed up for 15, 15, 8 months respectively with CCR. However, studies in Japan reported that two patients with non-bulky disease attained CR and long-time progression-free-survival(PFS) with surgical resection alone [9].Whether chemotherapy is necessary for this lymphoma type remains controversial. I also have to mention that despite good outcomes the current standard with 2 courses of non-intensive chemotherapy to treat such patients has accomplished with completely excised disease as data is lacking whether further de-escalation would increase risks of recurrence can't be explained.

In terms of prognosis, age is an important factor for LBCL. Children showed better response to chemotherapy and better outcomes than adults [16]. Besides, tonsillar lymphoma tends to be localized which may be a favorable prognostic factor compared with the involvement of other sites [17]. We hypothesized that the location in the tonsils plus early onset age and low LDH may be the main reasons for a better prognosis in LBCL with IRF4 rearrangement [18].However, the role of IRF4 rearrangement in prognosis needs to be further determined due to the rarity of reports of LBCLs with IRF4 rearrangement occurring in adult patients or in other sites.

Studies have shown that as an oncogenic protein,MUM1 makes LBCLs more aggressive and the prognosis is worse than MUM1-negative groups [19,20].However, the prognosis of LBCLs with IRF4 rearrangement is generally better [11].This contradictory result may due to the distinct clinicopathological features of LBCLs with IRF4 rearrangement. Pediatric doctors should be particularly alert to clinicopathological features in children with rapidly enlarging tonsils especially asymmetry plus regional lymphadenopathy. Once MUM1 is positive, LBCL is considered and FISH for the detection of IRF4 rearrangement should be performed.

Declaration of competing interest

None.

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