

Large B-cell lymphoma with IRF4 rearrangement

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Abstract

Large B-cell lymphoma with IRF4 rearrangement (LBCL-IRF4) is a new provisional entity in the WHO Classification of Tumours of Haematopoietic Neoplasms (revised 4th edition, 2017). It shows diffuse or follicular infiltrates of medium to large neoplastic B cells with an aberrant germinal centre phenotype with IRF4 positivity on immunohistochemistry and *IRF4* gene rearrangements found on fluorescence *in situ* hybridization (FISH). Here, we report a case of LBCL-IRF4 in a 30 year old female with asymmetrical tonsils. Microscopy showed partial infiltration by a diffuse, vaguely nodular proliferation of medium-to-large, highly proliferative B-cells and a background of follicular hyperplasia. The lesional cells were positive on immunohistochemistry for CD79, CD20, BCL2, BCL6 and IRF4, weak patchy positive for CD10 and had a high proliferative index. An IRF4 rearrangement was found on analysis by FISH. We have also included the pathological features of LBCL-IRF4 cases diagnosed in the Leeds Haematological Malignancy Diagnostic Service from 2017 to 2021.

Keywords diffuse large B-cell lymphoma variant; high-grade B-cell lymphomas; *IRF4* gene rearrangement; large B-cell lymphoma

Case report

A 30-year-old female presented with tonsillitis and was found to have asymmetrical tonsils on examination. She underwent tonsillectomy and the original Histological examination report was highly suspicious for non-Hodgkin's lymphoma. The case was referred to the Haematological Malignancy Diagnostic Service (HMDS) in Leeds for review. Microscopic examination demonstrated partial infiltration by a diffuse, partly vaguely nodular neoplasm of medium-to-large, highly proliferative B-cells with no underlying FDC mesh-works. The background was follicular hyperplasia. By immunohistochemistry, the tumour cells expressed an abnormal germinal centre (GC) B-cell phenotype with positivity for CD20 and BCL2 with combination of weak patchy CD10, BCL6 and IRF4 expression. The lesional cells had a Ki67 index of 80% (Figure 1). Tumour cells were negative on immunohistochemistry for CD23, CD30, CD5, CyclinD1 and LMP-1. Fluorescence *in situ* hybridization (FISH) was carried out and demonstrated an *IRF4* gene rearrangement. These results

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allowed for the diagnosis of the provisional entity of large B-cell lymphoma with *IRF4* gene rearrangement.

Discussion

Diffuse large B-cell lymphoma (DLBCL) is the most commonly diagnosed lymphoma globally. Whilst most of these cases are designated DLBCL not otherwise specified (DLBCL-NOS), around a fifth of cases can be categorized into one of 13 specific DLBCL variants. Large B-cell lymphoma with IRF4 rearrangement (LBCL-IRF4) constitutes a novel provisional entity included in the classification of lymphoid tissue recently proposed by the WHO in its fourth revised edition.¹ LBCL-IRF4 is a rare type of large B-cell lymphomas and accounts for 0.05% of cases. Literature reports it to be more common in children and young adults, with a median age of onset of 12 years.^{2,3} The disease has a predilection for the lymph nodes of the head and neck region and Waldeyer ring, although extra-nodal cases have been reported.^{4,5} Microscopically, there is an infiltrate of medium to large neoplastic cells with relatively open chromatin and small basophilic nuclei. The most common pattern of infiltration is diffuse, but a follicular pattern is also recognized.¹ A starry-sky pattern is usually not seen.

The neoplastic cells are positive by immunohistochemistry for mature B-cell markers CD20, CD79a and PAX5. There is usually strong, diffuse expression of BCL6 and IRF4 (MUM1). Two-thirds are positive for CD10 and BCL2. The proliferation index is high and neoplastic follicles do not show polarization.¹

The key cytogenetic feature is an *IRF4* gene rearrangement detected by FISH. The gene lies close to the telomere on the short arm of chromosome 6, and occasionally the rearrangement is not detected by current methods and in these cases, an *IGH* gene rearrangement can usually be found.^{1,3} There should not be any *MYC* or *BCL2* gene rearrangements.^{1,3}

Contrary to findings in the literature, local experience has shown that adult cases are relatively common, with a median age of onset of 48 years (range 6–78 years old), with a slight female predominance (Table 1). Our local case series demonstrates a predilection for the lymph nodes, tonsillar tissues and ileum. Microscopically, these appear as a large B-cell lymphoma with an abnormal germinal centre phenotype and a high proliferation rate. All local cases were positive by immunohistochemistry for mature B cell markers CD20 and CD79 and showed an aberrant germinal centre phenotype with all cases showing positivity for BCL6, CD10 and IRF4. Of these cases, one showed weak staining for BCL6, two

Presentation and pathological features of the index case and all large B-cell lymphoma with IRF4 rearrangement cases in Haematological Malignancy Diagnostic Service, Leeds 2017–2021. LN, lymph node; +, positive; -, negative; na, test not applied; FISH, fluorescence *in situ* hybridization

Case	Age	Sex	Sample location	Presentation	CD20	CD79	BCL2	CD10	BCL6	IRF4	KI67	CD5	CyclinD1	CD23	CD30	FISH	Cytomorphology	Pattern
1 index	30	F	Tonsil	Asymmetrically enlarged tonsil	+	+	+	+/-	+	+	80	-	-	-	-	IRF4 rearrangement, CEN6 normal signal pattern; CEN8 failed	Intermediate to large	Diffuse/follicular
2	6	M	Tonsil	Asymmetrically enlarged tonsil	+	na	-	+	+	+/-	30	na	na	na	-	IRF4 rearrangement, BCL2 normal, BCL6 normal	Intermediate	Follicular
3	36	M	Tonsil	Asymmetrically enlarged tonsil	+	+	+	+	+	+	60	-	-	-	-	IRF4 rearrangement; CEN8 normal	Large	Follicular
4	63	F	Parotid gland	Parotid mass	+	+	+	+/-	+	+	80	-	-	na	na	IRF4 rearrangement, CEN6 normal; CEN8 failed	Large	Diffuse/follicular
5	58	F	LN	Neck lump	+	+	+	+	+	+	80	-	+/-	-	-	IRF4 rearrangement; CCND1 no rearrangement, CCND2 no rearrangement; CEN6 normal	Intermediate to large	Diffuse
6	73	F	LN	Submandibular lump	+	+	-	+	+	+	80	-	-	na	na	IRF4 rearrangement, CEN6 normal	Intermediate	Diffuse
7	41	M	LN	Groin node	+	+	+	+	+	+	70	+	-	-	-	IRF4 rearrangement; CEN6 normal; CEN8 failed	Large	Diffuse/follicular
8	66	F	LN	Groin node increasing in size	+	+	+	+	+	+	90	-	-	na	na	IRF4 rearrangement, CEN8 normal	Large	Diffuse
9	9	F	Terminal ileum	Intussusception secondary to TI mass	+	+	-	+	+/-	+	70	na	-	-	-	IRF4 rearrangement; CEN11 normal	Large	Follicular
10	78	M	Distal ileum	Perforated ileum	+	+	+	+	+	+	90	na	-	na	na	IRF4 rearrangement, CEN8 normal	Large	Diffuse
11	76	F	Renal biopsy	Acute kidney injury	+	+	-	+	+	+	100	-	-	-	-	IRF4 rearrangement; BCL2 normal; BCL6 normal; CEN11 normal; CEN18 normal; CEN8 normal	Intermediate	Diffuse

Table 1

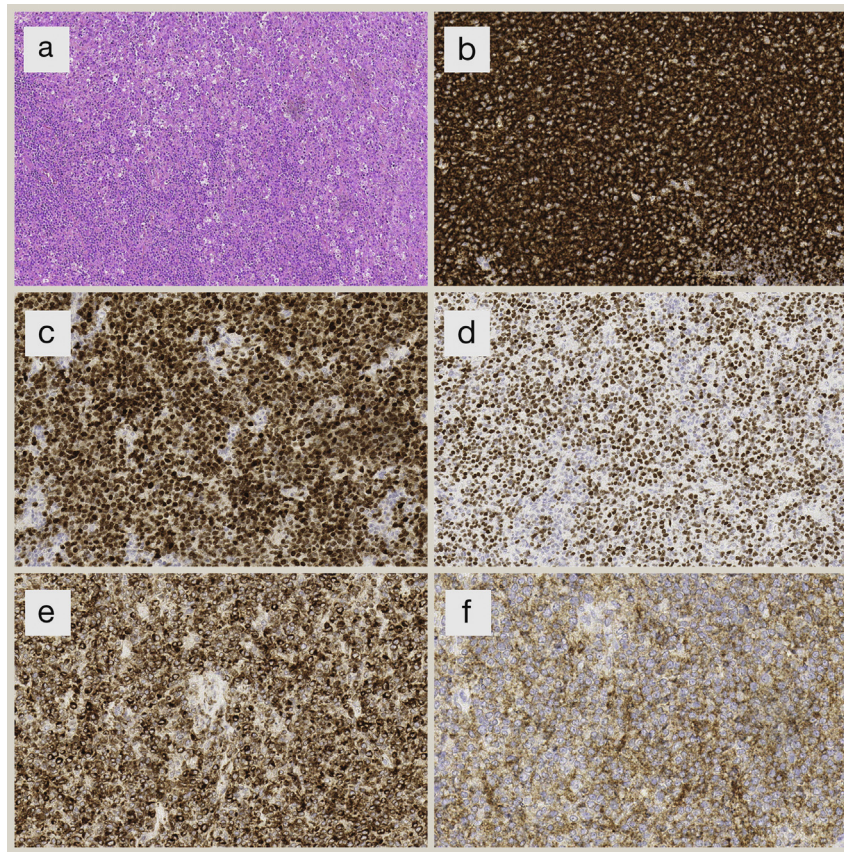


Figure 1 (a) H&E section of lymph node at x20 magnification showing infiltrate of medium to large neoplastic cells with relatively open chromatin and small basophilic nuclei. (b-f) immunohistochemistry showing positivity for CD20 (b), nuclear positivity for IRF4 (c), BCL6 (d), BCL2 (e) and weak positive CD10 (f).

showed weak staining for CD10 and one showed weak staining for IRF4. All cases showed an *IRF4* gene rearrangement on FISH and no *MYC* gene rearrangements were found.

A differential diagnosis would include paediatric-type follicular lymphoma (PTFL), particularly in a younger patient with a follicular morphology. The follicles in PTFL show serpiginous morphology with a starry sky appearance and the neoplastic cells are usually negative for BCL2 and IRF4, with no *IRF4* gene rearrangement on FISH.⁶ It is important to distinguish LBCL-IRF4 from PTFL as they are treated differently: LBCL-IRF4 has a favourable outcome after treatment (combination of immunochemotherapy with or without radiation), whereas PTFL tends to have a good prognosis with local management alone. In older patients, follicular lymphoma is a differential in cases with a predominantly follicular pattern. In others with a diffusely infiltrative pattern of high-grade neoplastic B cells with BCL2, BCL6 and CD10 staining, DLBCL and high-grade B-cell lymphoma (HGBCL) should be excluded. The neoplastic cells of HGBCL are more blastoid in appearance with more prominent nucleoli.⁷ The combination of CD10, BCL6 and IRF4 staining should trigger FISH analysis for an *IRF4* gene rearrangement.

Conclusion

Here, we reported a case of large B-cell lymphoma with an *IRF4* gene rearrangement in the tonsil of a 30 year old woman, with an accompanying case series. LBCL-*IRF4* is a rare specific variant of

large B-cell lymphomas and is an important differential to consider in cases of DLBCL or FL with aberrant germinal centre phenotypes. This rare entity, with a specific clinical presentation, is defined by the presence of a rearrangement of the *IRF4* gene. ◆

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Practice points

- Pathological features: Diffuse, diffuse and follicular or follicular infiltration, of medium to large cells.
- Phenotypic features: Aberrant GC B-cell phenotype CD20+ BCL2 + CD10± BCL6+ and IRF4+.
- Molecular features: Defined by the presence of a rearrangement of the *IRF4* gene.

Self-assessment questions

1. Immunoprofile of large B-cell lymphoma with *IRF4* rearrangement is:

- A. High grade ABC B-cell phenotype
- B. Low grade ABC B-cell phenotype
- C. Aberrant GC B-cell phenotype with IRF expression

Correct answer (C)

2. Which IHC combination is a clue for large B-cell lymphoma with *IRF4* gene rearrangement

- A. BCL2- CD10+ BCL6+ and IRF4-
- B. BCL2 + CD10± BCL6+ and IRF4+
- C. BCL2- CD10+ BCL6-and IRF4+

Correct answer (B)

3. *IRF4* rearrangement is characteristic of:

- A. large B-cell lymphoma with *IRF4* gene rearrangement
- B. Burkitt lymphoma
- C. Double hit lymphoma

Correct answer (A)