# Paediatric follicular lymphoma

Claudio Agostinelli
Manuel Rodriguez-Justo
Leticia Quintanilla-Fend
Alan Ramsay
Teresa Marafioti

## Abstract

Paediatric follicular lymphoma (PFL) is a rare variant of follicular lymphoma accounting for approximately 1%–2% of all paediatric non-Hodgkin lymphomas. PFL shows a male predominance with median age of onset varying from 7.5 to 14 years. PFL most commonly occurs in the head and neck region arising in lymph nodes or lymphoid tissue of Waldeyer's ring; extra-nodal localization is uncommon. Although the optimal clinical management remains unclear, most PFLs are low stage (i.e. localized) disease, and the prognosis is excellent with local excision leading to complete remission in the vast majority of the cases. As a rare lymphoid malignancy molecular and immunophenotypic studies on PFL are limited and both pathogenesis and biology are largely unknown. PFL is characterized by enlarged irregular lymphoid follicles showing high grade (grade 3) histological features. The germinal centres of these follicles are composed predominantly of cells showing "blastoid" morphology, with round to oval nuclei and small nucleoli. In most cases the neoplastic germinal centre cells lack both expression of BCL2 protein and the t(14;18) translocation but approximately one third of the cases can show weak expression of BCL-2 protein and a smaller percentage harbour BCL-2 rearrangements. In the clinical setting PFL has to be distinguished from reactive follicular hyperplasia and paediatric nodal marginal zone lymphoma.

**Keywords** differential diagnosis; immunohistochemistry; paediatric follicular lymphoma; paediatric lymphomas

***Claudio Agostinelli*** *MD Haematopathology Unit, Department of Experimental Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy. Conflicts of interest: none declared.*

***Manuel Rodriguez-Justo*** *MD FRCPath Department of Cellular Pathology, Haematopathology, University College London, London, UK. Conflicts of interest: MR-J is funded by the UCLH/UCL NIHR Comprehensive Biomedical Research Centre.*

***Leticia Quintanilla-Fend*** *MD Institute of Pathology, University of Tubingen, Germany. Conflicts of interest: none declared.*

***Alan Ramsay*** *MD FRCPath Department of Cellular Pathology, Haematopathology, University College London, London, UK. Conflicts of interest: none declared.*

***Teresa Marafioti*** *MD FRCPath Department of Cellular Pathology, Haematopathology, University College London, London, UK. Conflicts of interest: TM is funded by the UCLH/UCL NIHR Comprehensive Biomedical Research Centre.*

## Epidemiology and clinical features

Follicular lymphoma (FL) is the most common indolent lymphoma and accounts for about 20% of non-Hodgkin lymphoma (NHL) in the USA and the Western Europe.[1] It affects predominantly adults with a median age in the 6th decade and a male:female ratio of 1:1.7.[1] The cellular morphology, immunophenotype, and molecular (i.e. *IGVH* mutational status and mRNA profiling) features of FL all indicate its origin from germinal centre B-cells. Up to 80–90% of FL cases show the characteristic t(14;18)(q32;q21) translocation and the resulting *BCL2/IGH* rearrangement leads to the aberrant expression of the anti-apoptotic protein BCL2.[1] FL shows mainly lymph nodal involvement but spleen, bone marrow, peripheral blood, and extra-nodal sites are also commonly affected.[1] In the setting of extensive disease FL can also be seen at extra-nodal non-haematopoietic sites.[1] Most patients have widespread disease at diagnosis, with two third of the cases presenting in stage III or IV.[1] The disease course is typically indolent, but incurable with traditional therapies, and has a median survival of 8–10 years. In 25%–60% of cases, FL transforms into an aggressive diffuse large B cell lymphoma with a very poor prognosis.[1]

Paediatric follicular lymphoma (PFL) included in the 4th edition of WHO Classification of Tumours of Haematopoietic neoplasms as an FL variant that has distinct features from the adult.[1] PFL occurs in a young population and accounts for approximately 1–2% of all paediatric non-Hodgkin lymphomas (NHL).[2–8] The disease shows a male predominance with a male:female ratio of 4–6:1 and a reported median age at onset varying from 7.5 to 14 years in the major studies.[2–8] The head and neck lymph nodes as well as the lymphoid tissue of Waldeyer's ring are the most common sites involved by PFL. Extra-nodal localizations at first presentation are uncommon, but unusual involvement of testis, epididymis, gastrointestinal tract, kidney and parotid gland have been also reported.[2–8] Such rare cases are usually associated with a poor prognosis and shorter survival.[9] Most patients with PFL present with low stage disease; almost 70% of the cases are stage I at onset. Although optimal clinical management remains undefined, the majority of cases achieve complete remission after local excision and have an excellent prognosis.[2–8] PFL shows morphological, immunophenotypic and molecular features (discussed in details below) that are distinct from the classical adult counterpart although it must be added that a small group of adult FL shows some features similar to that of PFL. Whether there are molecular events in common between PFL and the BCL-2 negative adult FL remains to be clarified.

## Histological and phenotypic features

PFL shows preferential involvement of head and neck lymph nodes and of Waldeyer's ring lymphoid tissue (tonsil and/or adenoid). Extra-nodal presentations have been reported, with testicular disease being the most frequent.[3–8]

From the studies in the literature, in the vast majority of PFL case, the neoplastic cells show high grade (grade 3) histological features and are described as small to medium-sized proliferating "blastoid" cells with round/oval nuclei, finely clumped chromatin and small nucleoli. Their morphological appearance is distinct from that of normal germinal centre centroblasts and centrocytes. However, some morphologic and immunophenotypic differences

 

in PFL arising in the most common anatomic sites (lymph node, tonsil and testis) have been reported.[6]

Lymph nodes involved by PFL show effacement of the normal architecture by large expanded and irregular or serpiginous follicles with attenuated mantle zone (Figure 1). In occasional cases confluent follicles can give rise to a diffuse growth pattern.[4–6] The germinal centres (GC) in the follicles lack polarization and are commonly composed of a monotonous proliferation of small to medium-sized blastoid cells with round to oval nuclei, finely clumped chromatin and small nucleoli.[6] Using the grading system for typical ("adult") FL, the histology would be classed as grade 3A (Figure 1). The blastoid cells should not be confused with small centroblasts and/or large centrocytes.[6] Tingible-body macrophages are often retained conferring a "starry-sky" appearance to the germinal centres; this differs from typical FL, where tingible-body macrophages are usually lost, and can lead to diagnostic confusion with reactive follicular hyperplasia.[4–6] In some PFL cases the follicles are surrounded by a rim of clear cells suggesting a degree of monocytoid differentiation. Involved nodes can show residual small reactive follicles adjacent to the enlarged neoplastic follicles that simulate the picture of a "node within a node". On immunohistochemistry, the abnormal germinal centers strongly express CD20, CD10 and BCL-6; with minimal spread of the atypical cells into the interfollicular region (Figure 2).[6] The abnormal germinal centre cells are commonly BCL2 negative (Figure 2), but weak positivity or heterogeneous staining is reported under 20% of cases.[6] IRF4/MUM1 is mostly negative in the germinal centres (Figure 2).[6] IgD highlights attenuated mantle zones and may be useful in cases where the morphology shows a vague diffuse pattern (Figure 2).

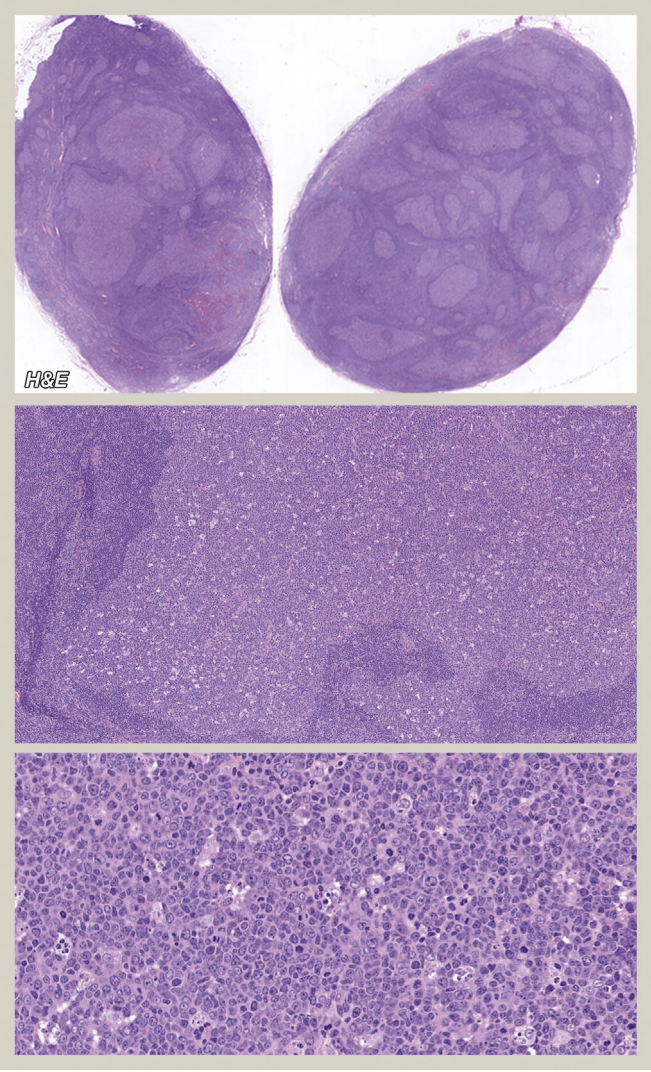


**Figure 1** Lymph node: large expansile or irregular/serpiginous follicles with attenuated mantle zone, with germinal centres lacking polarization, and consisting of monotonous proliferation of small to medium-sized blastoid cells with round/oval nuclei, finely clumped chromatin and small nucleoli; tingible-body macrophages are often retained conferring a "starry-sky" appearance.

PFL involving the Waldeyer's ring shows a follicular growth pattern with large expanded atypical follicles surrounded by mantle zones and the "starry-sky" appearance of the tingible-body macrophages is normally maintained. The cytological features include cases (approx. one third) with abnormal germinal centres composed predominantly of typical centroblasts and others with "blastoid" cells.[6] The germinal centre cells in tonsillar/adenoidal PFL are also strongly positive with CD20 and BCL6 but in contrast to nodal disease CD10 is expressed in only 60% of the cases; weak CD10 labelling can also be seen. IRF4/MUM1 is mostly positive at this site, and BCL2 is more frequently detected (approximately 60% of cases).[6]

PFL of the testis consists of nodular groups of closely-packed lymphoid follicles, infiltrating between the seminiferous tubules and lacking well-defined mantle zones. The proliferating cells show the morphology of centroblasts and tend to be confined to the atypical follicles.[6] The immunophenotype of the neoplastic cells is characterized by CD20, CD10 and BCL6 expression but a lack of BCL2 and IRF4/MUM1.

In all instances (i.e. nodal, tonsil and testicular PFLs) the neoplastic follicles show a moderate to high Ki-67 proliferation fraction in the germinal centres without any evidence of polarization (Figure 2).

CD21 staining highlights expanded irregular but not fragmented follicular dendritic cells (FDC) meshworks in the follicles of the nodal type and more nodular networks in the atypical follicles of the tonsil and testis type.

PFL frequently expresses intracytoplasmic IgM and shows light chain restriction (slightly predominance of kappa light chain) (Figure 2).

## Molecular biology

PFL shows genetic features distinct from its adult counterpart and molecular events associated to its development have not yet been properly defined. In the majority of the cases IgH and/or IgK gene rearrangements are detectable by PCR. Cytogenetic analysis demonstrates absence of t(14;18)(q32;q21) translocation and *BCL2/IGH* rearrangement in most instances[3–8] with the exception of approximately 20%–30% of cases in which *BCL2/IGH* rearrangement is found coupled with expression of BCL-2 protein.[3–8] The latter cases include children older than 12 years and they frequently present with widespread disease (stage III and IV) and appear to have a more adverse outcome.[3,5] Rearrangements of *BCL6* and *MYC* genes are generally not detected by FISH analysis in PFL.[6,10,11] In cases involving