Reviewer's report

Title: Primary follicular lymphoma of the epididymis t(14;18)(q32;q21)/IGH-BCL2-positive: a case report

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Reviewer: Russell Ryan

Which of the following best describes what type of case report this is?: Unexpected or unusual presentations of a disease

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:

The authors present a case of primary follicular lymphoma arising in the epididymis of an elderly male. The tumor was proven to have a t(14;18) rearrangement by both PCR and FISH testing. As they note, cases of primary epididymal / paratesticular follicular lymphoma have been only rarely reported in the literature. Those cases which have been reported were typically in young adult males, and lacked rearrangements of BCL2 or BCL6. Thus, even within the rare category of primary paratesticular follicular lymphoma, this case has unique features, which will make a meaningful contribution to the literature.

My most significant concern about this work, as written, is the authors’ statement that BCL2 protein was not expressed in this case, despite the presence of an IGH-BCL2 rearrangement. This claim is made on the basis of negative
immunohistochemistry for BCL2. However, there is a well-recognized phenomenon by which anti-BCL2 antibodies may fail to detect expressed BCL2 protein in lymphomas with BCL2 rearrangements, due to somatic hypermutation of the BCL2 gene sequence encoding the epitope recognized by the antibody. In such cases, testing with a different antibody raised against a different BCL2 epitope usually demonstrates expression of the protein (see Schraders, M., de Jong, D., Kluin, P., Groenen, P. and van Krieken, H. (2005), Lack of Bcl-2 expression in follicular lymphoma may be caused by mutations in the BCL2 gene or by absence of the t(14;18) translocation. The Journal of Pathology, 205: 329–335. doi: 10.1002/path.1689). The authors need to recognize this possibility in their discussion, and ideally should conduct staining on this case with an alternative BCL2 antibody. The authors should also state the manufacturer and clone of the BCL2 antibody they used.

The authors report that their case is grade 2 under the WHO system. However, the preferred classification in the 2008 WHO is “follicular lymphoma, grade 1-2”, since grades 1 and 2 of the older system were not found to have a meaningful biological distinction.

Several statements made in the discussion are confusing, or seem inaccurate as phrased. The manuscript would benefit from review by a copy editor with strong English language skills.

“Until today, adult primary lymphomas of testis and epididymis have not been well characterized yet.” – As the authors note in their references, several large studies of primary testicular lymphoma have been published over the past 4 decades, so this statement seems inaccurate. Case series of primary paratesticular / epididymal lymphomas are indeed smaller and less frequent.

“Usually, [follicular lymphoma] presents with lymphadenopathy, but a minority of cases presenting primarily with extranodal disease are reported. Extranodal sites include gastrointestinal tract, skin, ocular adnexal, and breast [20]. These lymphomas phenotypically and genotypically are similar to those of nodal follicular lymphoma, in which bcl-2 protein is usually expressed and a translocation involving bcl-2 and IgH genes is frequently detected [20].” - This statement does not do justice to the unique features of “follicular lymphomas” presenting as primary disease in different extranodal sites. For example, cutaneous “follicular lymphoma”, as identified in the past, included many indolent cases which lacked BCL2 rearrangements, and are now considered a separate entity in the latest WHO (PCFCL). Primary gastrointestinal FL includes many cases which have the t(14;18), but behave in an indolent manner and do not spread to other sites (similar in many respects to the authors’ paratesticular case). Primary thyroid FL includes one subgroup of cases which are clinicopathologically similar to systemic FL (BCL2 rearranged, progressive, low grade histology) and another which is more similar to PCFCL and primary testicular FL in that it often has high grade histology, lacks BCL2 rearrangement, and does not progress systemically. It would be very helpful for the authors to review this spectrum of extranodal “follicular lymphomas” and place their case in context (e.g. most similar to the indolent, BCL2 rearranged gastrointestinal FL). An outstanding and up-to-date
resource in this area is Judith Ferry’s 2011 book “Extranodal Lymphomas”.

“Bacon et al. described 5 cases of primary follicular lymphoma of the testis and epididymis in adults histologically characterized by small neoplastic follicles in a sclerotic background, and phenotypically by CD10 and Bcl-6 expression and not by Bcl-2 expression and by t(14;18)(q32;q21)/IGH-BCL2 and BCL6 gene rearrangements” - The phrasing of this statement is confusing. The cases of Bacon et al showed immunophenotypic expression of CD10 and BCL6, lacked immunophenotypic expression of BCL2, and lacked t(14;18)(q32;q21)/IGH-BCL2 and BCL6 rearrangements.

The statements made in the “conclusion” section of the main text and abstract are overly broad, and are not clearly supported by this single case report. This section should be extensively revised. As noted, larger studies utilizing multiple alternative antibodies for the Bcl-2 protein have found that Bcl-2 protein in almost always expressed in cases of lymphoma with the t(14;18), and the author’s statement “First, the expression of BCL2 protein is not specifically correlated with IgH/bcl2 gene rearrangement but may be expressed independently by presence or absence of the relative translocation” is not proven by the evidence presented here.

The statement “Second, there is no correlation between prognosis and the presence of t(14;18)(q32;q21)/IGH-BCL2 translocation, because adult patients with primary follicular lymphoma of the testis and epididymis experience an excellent prognosis by presence or absence of the bcl-2 gene rearrangement independently” is too strong, as the apparently good outcome of a single patient with paratesticular FL with t(14;18) cannot be used to draw statistically significant conclusions about prognosis for this group as a whole. Most FL with t(14;18) presenting in this site likely represents secondary involvement by systemic/nodal FL, which would have a worse prognosis than the primary paratesticular FL reported to date. The Pezzella paper presumably included mostly nodal / systemic FL in both groups, and is not directly applicable here. I’d recommend that the authors replace this conclusion with a statement that based on their case, diagnosticians cannot conclude that any FL presenting in a paratesticular site and bearing the t(14;18) represents secondary involvement by systemic FL.

The final statement “Taken together, the findings here reported demonstrated that t(14;18)(q32;q21)/IGHBCL2-negative or t(14;18)(q32;q21)/IGH-BCL2-positive primary follicular lymphomas of the testis and epididymis, represent the same clinicopathologic entity and are characterized by clinically indolent localized disease with good clinical outcome in young and old males” again is too strong, and cannot be supported by this single case report. I would recommend that the authors replace this with a statement saying that primary paratesticular FL with t(14;18) could represent either a variant of the previously reported t(14;18) negative primary paratesticular FL, or a distinct biological entity (perhaps more closely related to indolent BCL2 rearranged FL in other sites), and that reporting of additional cases in the future would be helpful in resolving this question.
Quality of written English: Needs some language corrections before being published

Declaration of competing interests:
I declare that I have no competing interests