The Daily Dose: Study Tips for Exam and Board Preparation

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The Daily Dose: lymphoid, histiocytic and granulomatous disease(s)

I was asked about lymphoid and histiocytic lesions and decided to do a little extra leg work this evening. I am not as skilled with lymphoproliferative disorders, and the topic is so broad that I think it would be impossible to cover everything in a short period of time.

I would offer the following recommendations to help:

1. Identify the lesion first as something lymphoproliferative or as an atypical lymphoid proliferation
2. Try to decide if the cells are small cells or large cells (use a normal lymphocyte nucleus as a standard measuring tool)
3. Plan to perform and explain immunohistochemistry on all of these cases (more on this in a bit)
4. Plan to consider flow cytometry (and remenber flow cytometry and submission of tissue in RPMI or equivalent medium)
5. Plan to consider cytogenetics in most of these cases, with some translocations and abnormalities more common

I don't feel it's feasible to communicate all the stains and cytogenetic tests to consider, so I think it's wise to locate some kind of summary or text; I think a skim o each chapter Ioachim's *Lymph Node Pathology* can be helpful.

Here are my cursory thoughts:

Choose an IHC panel that will provide both B and T cell markers, looking for coexpression; this might include:

- CD3, CD5, CD10, CD20, CD79a should give you a broad picture of B and T cell expression or coexpression
- CD138 may aide in identifying plasma cell lesions (especially if hidden in a sea of other lymphoid cells
- pattern of bcl-2 expression can assist with reactive versus neoplastic
- bcl-6 may aide in determining if the lesion is malignant
- CD15 and CD30, along with EBER (for EBV) may be helpful if you're considering a variant of Hodgkin lymphoma
- some large cell markers like CD30 may be helpful
- CD21 and CD23 may aide in evaluating the morphology of germinal centers and meshwork
- bcl-1 (cyclin D1) is useful to help identify mantle cell lymphoma
- c-myc expression or an associated translocation may aide in deciding on Burkitt lymphoma or high grade (diffuse large) B cell lymphoma with Burkitt features

It may be enough to decide that it's a lymphoma and describe a panel and simply favor either small cell lesion (like CLL/SLL or mantle cell lymphoma) or a large cell lesion (like diffuse large B cell lymphoma) or plasma cell features (plasmablastic lymphoma in HIV, immune suppression or plasmacytoma or myeloma)

The translocations to consider and read a little about would be those involving c-myc (chromosome 8 with chromosome 2 and some others) and variations on chromosome 11, 14, 18 translocations that include bcl-1, immunoglobulin heavy chain and bcl-2 loci... this is something to read about regularly.

As far as the histiocytic lesions are concerned, I was asked about Langerhans cell histiocytosis (LCH), Kikuchi-Fujimoto Disease, two articles (cases) on Rosai Dofrman Disease, and one on Castleman's Disease.

There are any number of articles on this, and I like (for a broad overview):

- Hicks et.al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:S42-66
- Kademani et,al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:699-701 Kalman et.al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:e124-e126
- Hutchinson et.al. Arch Pathol Lab Med. 2010; 134:289-293
- Cronin et.al. Adv Anat Pathol 2009;16:236–246)

Look for these in any lymphoid lesion:

- plasma cells (see the discussion above, as well as some variants of Castleman's)
- eosinophills and histiocytes with 'reniform' or kidney-shaped or indented nuclei (LCH), but also present in lesions like Kimura Disease and angiolymphoid hyperplasia with eosinophilia AND so-called 'TUGSE' (traumatic ulcerative granuloma with stromal eosinophilia which may have 'ugly' features that may make you think about EBV or CD30 related mucocutaneous ulcers
- eosinophils may also be identified in some variants of Hodgkin lymphoma, so look for Reed-Sternberg (owl eye) cells and 'popcorn' cells
- necrosis should make you think of a wide diagnosis including infectious (like cat scratch, Mycobacterial disease, etc.) and Kikuchi-Fujimoto (necrosis + histiocytes)
- look for emperipolesis (engulfment of lymhocytes or plasma cells by large histiocytes) to consider Rosai Dorfman Disease (I have a hard time finding this myself)

I sent a few cases, which pair with most of the above articles and include:

- EBV related mucocutaneous ulcer
- nodular sclerosing Hodgkin lymphoma
- Langerhans cell histiocytosis
- Rosai Dofrman Disease
- Kikuchi Fujimoto Disease

Even though I provided the answers and all the IHC used in the cases, I asked the (potential) respondent to write diagnostic lines for each case, and what I suggested tp do is look at each IHC stain or panel and communicate what kind of information that stain may be providing in those cases; an example might be:

LYMPHOMA, MOST CONSISTENT WITH DIFFUSE LARGE B CELL LYMPHOMA

- CD3 and CD5 expressed in T cells and coexpressed in large cell population, consistent with B cell malignancy
- CD20 and CD79a are diffusely expressed in the abnormal large (B) cells, consistent with a B cell malignancy
- bcl-2 is expressed in residual germinal centers, consistent with a malignancy (versus a reactive lesion)
- Ki-67 is approximately 50%, consistent with a high grade lesion
- c-myc not expressed in lesion cells by IHC; t(2;8) is not identified, favoring against a Burkitt phenotype
- ALK-1 and CD30 are not expressed in lesional cells, favoring against anaplastic large cell lymphoma
- CD15 and CD30 are not expressed, favoring against Hodgkin lymphoma

and so on

Regarding granulomatous inflammation, I felt I could answer this question much more easily, and although I don't have any specific histology cases in this area like the others I sent, I provided a few thoughts that I think should help:

- First, look in the text books and study granulomas; they're sometimes hard to find especially when they're "loose" or "diffuse"
- If you see 'tight' granulomas without necrosis, think about things like sarcoidosis
- If you see granulomas with necrosis think about infectious diseases and then perform fungal stains (PAS-F and GMS) to identify hyphae or spores, and AFB (Fite or other stains) to try to identify Mycobacterial disease; also consider gram stain though I have yet to have any luck with it... serology is probably better
- If you have a polarizing lens, look for birefingent material; granulomas can be present in many foreign body lesions
- Some cases of granulomatous inflammation may also include things like Wegener granulomatosis (a short read in a text like Neville and Damm should help), inflammatory bowel disease (Crohn's et.al.) and in some cases the oral granulomas will have associated eosinophil (micro)abscesses - there should be a pertinent clinical history and inquiry

I don't believe we have to be afraid to consider IHC in these cases if there's suspicion for (epithelioid) histiocytes or granulomas; traditionally CD68 has been used, but CD163 may be a more sensitive stain.

I would leave it here, for this discussion. These types of lesions can and should be simpler than all the lymphoid and histiocytic lesions. I don't have any specific cases put together, but one should be able to skim Neville and Damm or comparable text for what is needed.