HOST DEFENSE

SMALL GROUP PROBLEM SOLVING SESSION

B-CELL, T CELL, AND B&T CELL DEFICIENCIES

Small Group Classrooms

LEARNING GOALS

You will be able to identify the implication(s) of **impaired/defective** T & B-cell function.

To achieve this goal, you will be able to:

- Predict the clinical implications of antibody deficiency.
- Predict the clinical implications of T cell deficiency.
- Predict the clinical implications of a combined B & T cell deficiency
- Develop appropriate therapeutic strategies for each type of defect

BACKGROUND READING

1. Janeway:8th edition. Pp 470-478, 488-490 and Figs. 11.11 and 13.42. Do NOT memorize any Table!
2. Reading the posted New England J of Medicine & Science articles on the HD website will make all 4 cases much easier to understand. .**DO NOT WORRY ABOUT THE TECHNICAL DETAILS IN THE ARTICLES-you won't be tested on them. WORRY ABOUT THE CONCEPTS.**

DEVELOPED BY

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For the remaining small groups, your room assignment may change. Changes will be posted on the classroom doors.

HOW TO SUCCEED IN SMALL GROUPS

Before coming to class:

1. Read assigned chapters/ pages and develop answers for **ALL** the questions in the 4 clinical vignettes

During the Small Group Session:

2. Each small group (**should be 4-5 peers- please do not sort yourselves into large groups-you will learn much less**) should discuss the four case studies and decide the best solutions to the specific integrating questions associated with each case.

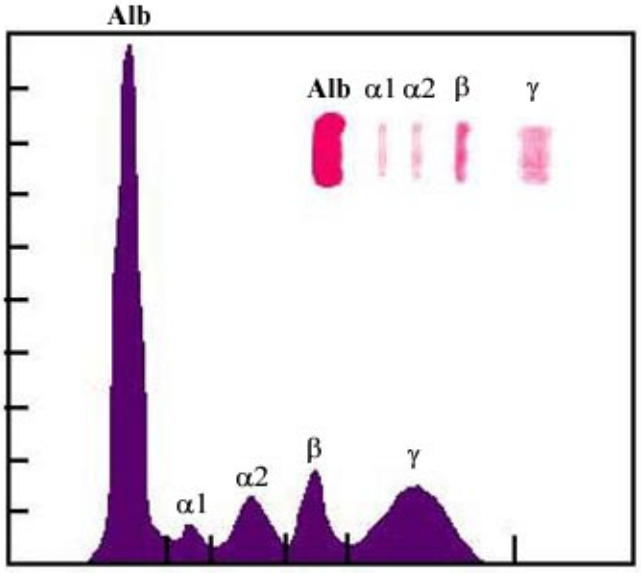
3. After approximately an hour of discussion by the subgroups, the facilitator will recapitulate the answers to the integrating questions by selecting a subgroup to present a synthesis of their relevant discussions to the entire group. Facilitators will select, at their discretion, a small group for the discussion of the individual cases.

4. History has shown that students who don't contribute to the Small Groups do not do well in the Course (remember that about 25-30% of the final comes from small groups!) and also have been assaulted by their fellow group members

5. At the end of the session, a master answer sheet will be posted on the Host Defense website.

CASE 1

An eight month old male developed a fulminant bacterial pneumonia but survived after prolonged use of intensive intravenous antibiotic therapy. The nurses noted that the venous puncture sites where the lines for antibiotic therapy were placed rapidly became infected. This infant was the product of a normal, full term pregnancy and developed normally until this pneumonia occurred. A scout x-ray that imaged the upper respiratory tract to the lower abdomen revealed the presence of thymus, pneumonia, and a curious absence of 'tonsillar tissue' Routine laboratory testing during his illness revealed the expected rise in neutrophil counts in his peripheral blood during this infection; but it was noted that the serum protein electrophoresis had almost no protein fraction migrating to the globulin range. A FACS (technique discussed in a previous small group) analysis of his peripheral blood lymphocytes is pending



This serum protein electropheresis is **NORMAL.** The patient's wasn't.

1. Is the patient's gender and isolated abnormal laboratory finding related to his severe infection?

   Are his future sisters at risk?

   Outline the rationale for ordering the serum protein electrophoresis, predict how it would differ from the normal above and discuss what CD markers should be included in the FACS analysis.

2. Why did this child do so well during the first eight months of life?

   Were his leukocytes (neutrophils), which appeared ‘normal’ in response to this infection, really functioning optimally now?

3. Recurrence of certain types of bacterial infections are important clues to several specific immunologic defects - discuss what defense mechanism(s) some bacteria use to escape killing by neutrophils and why they are relatively resistant to standard antibiotic therapy?

4. Once the specific B-cell defect known, what type of therapy may be lifesaving?

CASE 2

A one month old female, the 7th child in the family, was noted to have a perforate nasal septum. The pediatrician, in an attempt to screen for associated upper respiratory tract congenital abnormalities, ordered several x-ray views of her throat, sinus and chest. An alert radiologist noted that there was neither thymus nor tonsillar shadows. Two weeks later the child developed a bacterial pneumonia and required admission and intensive antibiotic therapy. Six weeks later, she developed a severe disseminated fungal infection. Laboratory examination revealed that her white cell lineages (neutrophils, monocytes, basophils and eosinophils) were normal but there were no detectable lymphocytes in her peripheral blood. The child had a very slow response to aggressive anti-fungal therapy. Serum protein electrophoresis and FACS analysis of the child's peripheral blood cells are pending.

1. Is the clinical observation that neutrophils and platelets were normal but her lymphocytes were markedly reduced in the peripheral blood helpful in suggesting where the actual defect in cell development in this patient might be? For help, look at the figure on p1791 of the posted New England journal Perspective article.

   Predict and justify the results of the electrophoresis and FACS.

2. What studies on this patient's lymphocytes could be done that might define the specific immune defects present?

   Set up a FACS analysis of aspirated bone marrow that could clarify where the defect might be.

3. Using the figure on page 1791 of the *New England J Medicine* "perspective" article posted on the HD website, predict the probable deficiency and the types of infections that would be found:
    - If this patient had no detectable B, T or NK cells.
    - If this patient had a a RAG deficiency
    - If this patient had a JAK-3 deficiency
    - If this patient had a adenosine deaminase deficiency

4. Why is identification of a specific immunopathologic defect and a specific immunologic diagnosis important for the child's immediate treatment, prophylaxis and definitive therapy?

   Ten years later the patient was taking no medications, doing well in school and even thought Justin Bieber was "very cool". Does this fortunate outcome have anything to do with being a member of a large family?

CASE 3

A twenty-three year old RN, an intravenous drug abuser, develops 3 episodes of acute bacterial pneumonia within three months. All episodes require hospitalization and intravenous antibiotics. She insists that she uses only her own needles (appropriated from her employer). She has several striking laboratory abnormalities: an elevated number of normal appearing lymphocytes in her peripheral blood, a normal number of neutrophils, but a very low serum total protein and an abnormal serum protein electrophoresis. A FACS analysis has already been done and it revealed a normal amount of CD3 lymphocytes and slightly elevated number of B cells. Unfortunately, the FACS operator forgot to set up the analysis for the CD3 subsets of lymphoid cells in the peripheral blood.

1. The diagnosis seems straight forward-she has HIV infection (or does she)?

   If she does not have an AIDS related illness, where might the basic immune defect be?

2. The patient then suffered a ruptured spleen during a motor vehicle accident. The alert internist requested a pathologic report on the organ after its removal at surgery. What were the most likely immunohistologic findings?

3. She obviously does not have x-linked agammaglobulinemia. Where are the possible defects in her B-cell response sequence? Before you decide on the mechanism, you remember to ask for a repeat FACS analysis that will detect T subsets. What reagents would you want the technician to use? To the amazement of her physician, the repeat FACS showed that the % of CD3,8 cells in her peripheral blood was elevated.

   a. Postulate what his physician was expecting on the FACS.

   b. Discuss treatment strategies to ameliorate the immunodeficiency (Don't get frustrated-the precise mechanism(s) of this disease are not known, but use your immunologic logic to speculate)

4. Ultimately this patient died of a lymphoma- a neoplasm of lymphoid tissue. Is this a surprising complication?

CASE 4

A 26 month old male presented with almost the identical clinical and laboratory findings as the girl in Case #2. This child however was adopted, the father was unknown and the mother had been killed in a car accident. No siblings were known to exist.

1. How does the ill-starred, additional history about this child change your treatment strategies?

2. Outline the possible ways if any that a cure might be possible.

3. After an extensive search of the national data base for potential bone marrow donors no suitable donor could be found. Gene therapy was then considered after a specific defect was found. Outline the technique(s) and rationale for the treatment modality. This can be found in the articles on the HD web site.

4. The child undergoes gene therapy and recovers. He does very well for three years and had no serious infections. Then, on a routine blood count, very high numbers of lymphocytes are found and the spleen is enlarged. Curiously, a very large proportion of the lymphocytes have a γδ T cell receptor. Convince your peers, and ultimately your facilitator, that you understand how this happened. You will only be able to do this if you read the posted article.

5. Be sure, as a group, you discuss the pros and cons of gene therapy.

5. In honor of George Santayana and serendipity

How are chickens and B cell deficiencies related?

Glick B. The bursa of fabricius and antibody production. PhD dissertation. Columbus, Ohio: State University, Columbus, 1955:1-102