Histology of hypersensitivity including the role in Tuberculosis

Answer Sheet

Type I – e.g. nasal polyp

Q1 Where are the IgE antibodies located?

A1. IgE antibodies are bound by their Fc portion to high affinity Fc receptors expressed on Mast cells and basophils.

Q2 What is the likely allergen (antigen)?

A2 Pollen, house dust mite and faeces (Der P1 contained in faeces of Dermatophagoides pteronyssinus), domestic pets or moulds.

Q3 How does the oedema fluid develop?

A3 Antigen binds to IgE antibody on the surface of mast cells and activates them. Activation of mast cells leads to release of vasoactive mediators (including histamine, Leukotrienes C4, D4 and E4 and prostaglandin D2), which cause vasodilatation and increased vascular permeability. Fluid leaks out of the blood vessels into the tissue spaces forming oedema.

Q4 Give examples of the chemotactic and vasoactive mediators that are released?

A4

<table>
<thead>
<tr>
<th>Chemotactic mediators</th>
<th>Vasoactive mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene B4</td>
<td>Histamine</td>
</tr>
<tr>
<td>PAF</td>
<td>Platelet activating factor (PAF)</td>
</tr>
<tr>
<td>Cytokines e.g. (1) TNF-α recruits other leucocytes; (2) IL-4 recruits eosinophils</td>
<td>Leukotrienes C4, D4 and E4 Prostaglandin D2</td>
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</tbody>
</table>

Q5 What would you expect the symptoms to be? (On the basis of what you see, or perhaps your own experience or that of a colleague who may have Hay Fever)
A5 Nasal irritation with water rhinorrhoea ("runny nose") and/or nasal blockage due to the large size of some polyps hanging down in the nasal air passages. Also itchy eyes.

**Type II – e.g. Hashimoto’s thyroiditis**

Q6 Is there evidence of tissue destruction? Is it a cytotoxic process?

A6 Yes, there is evidence of tissue destruction – the thyroid follicles are small and lined by fewer epithelial cells. In some areas, thyroid follicles are absent.

Yes, this is a cytotoxic process mediated by the immune system.

Q7 What type of T lymphocytes would you expect to be involved?

A7 CD4+ (helper) T lymphocytes interact with B lymphocytes and stimulate the secretion of antithyroid antibodies, which activate antibody dependent cytotoxicity mechanisms. Also the helper T lymphocytes induce the formation of CD8+ (cytotoxic) T lymphocytes which can directly kill the thyroid follicular epithelial cells.

Q8 Is the lymphoid infiltrate organised into lymphoid follicles with germinal centres?

A8 Yes – lymphoid follicles with germinal centres are visible in the sections provided.

Q9 What is the mature cell produced by lymphoid follicles with germinal centres? Can you see many examples of this mature cell in the section? What is its effect on thyroid epithelium?

A9 B lymphocytes mature into plasma cells (and some memory cells), which secrete antibodies, in this case resulting in increased anti-thyroid antibody production and destruction of the thyroid follicular epithelium.

Q10 What is likely to be the effect of these changes on plasma levels of thyroxine and tri-iodothyronine? Why do the remaining thyroid acini (or thyroid follicles) have an “over-stimulated” appearance with little colloid and tall epithelium?

A10 Plasma levels of thyroxine (T4) and tri-iodothyronine (T3) are decreased due to extensive loss of the thyroid epithelium that makes them.

The low plasma levels of thyroxine (T4) and tri-iodothyronine (T3) stimulate the anterior pituitary to secrete Thyroid Stimulating Hormone (TSH) as part of the feedback system, and the high levels of TSH “over-stimulate” the remaining thyroid follicles, so that they have little colloid and tall epithelium. Some patients may have auto-antibodies capable of stimulating the TSH-receptor as well.
Type III – e.g. Systemic Lupus Erythematosus

Q11 What makes up an ‘immune complex’?

A11. An immune complex is composed of antibodies and antigen molecules bound together to form large aggregates of many antibodies and antigens stuck together. These are variable in size – the size depends largely on relative antigen and antibody concentrations.

Q12 Where (in which structures) are immune complexes deposited?

A12 Immune complex deposition is determined by several factors, including the physicochemical properties of the complex (e.g. cationic antigens bind avidly to the basement membrane of kidney glomeruli) and anatomical factors (capillaries in renal glomeruli and synovia are where plasma is ultrafiltered). In terms of organ distribution common sites include: renal glomeruli, joints, and skin, (and sometimes heart, and serosal surfaces).

Q13 How do deposited immune complexes trigger an inflammatory response?

A13 Immune complexes activate complement, thus recruiting and activating inflammatory cells (particularly neutrophils and macrophages – the extra cells in the glomeruli in this form of glomerulonephritis) by binding via their Fc or C3b receptors.

Type IV – e.g. Tuberculosis

Q14 What makes mycobacteria different from other bacteria?

A14 Mycobacteria have an unusual waxy cell wall compared to gram-positive and gram-negative organisms – it is very hydrophobic and has a high lipid content. The wall enables mycobacteria to survive inside macrophages as it renders them resistant to the usual concentrations of lysosomal enzymes. The wall also limits the rate of nutrient transfer into mycobacteria so they are slow growing in comparison to other bacteria.

Q15 In a case of lung infection by TB, where are the organism’s antigens first presented to the immune system? How do the antigens get there?

A15 Antigen is presented in the lymph node. Alveolar macrophages that have ingested mycobacteria are carried by lymphatics to the lymph node.

Q16 What sort of T cells are involved in the response?
A16 CD4+ T lymphocytes (Th1 cells) produce cytokines, in particular IFN-γ, which activate macrophages so that they can kill mycobacteria, leading to the transformation of macrophages into epithelioid cells and multinucleate giant cells.

Q17 Why are HIV infected patients particularly susceptible to mycobacterial infection?

A17 HIV infection results in the death of CD4+ T lymphocytes, producing an overall decrease in the number of CD4+ T lymphocytes in the blood – the key cell for the response to mycobacteria.

Q18 What is a granuloma?

A18 A granuloma consists of a collection of macrophages. In the granuloma, the macrophages are often transformed into epithelioid cells. The granuloma is usually surrounded by a collar of lymphocytes.

Q19 What causes the tissue damage (caseation) in TB? Is it the virulence of the organism or the host immune response?

A19 The host immune response causes the tissue damage – a key property of type IV (delayed) hypersensitivity.

**Process identification & Report Writing**

There are two different types of follicle-like structures within the substance of the spleen. There are normal lymphoid follicles, some with germinal centres in the white pulp. There are also numerous granulomata typical of tuberculosis, some with central caseating necrosis, epithelioid macrophages and a few giant cells, with a rim of lymphocytes. A Z–N stain could be performed to confirm the presence of tubercle bacilli (acid and alcohol-fast red rods on a blue background). The scattered pattern of numerous small granulomata indicates miliary spread of tuberculosis.

**The pathological process is type IV delayed hypersensitivity (also called granulomatous chronic inflammation) in response to tuberculosis of the spleen due to miliary tuberculosis.**

Image Map: A_TB_ML_SP_03