Secondary Immunodeficiencies (Acquired Immunodeficiencies): Malignancy, Infections and more

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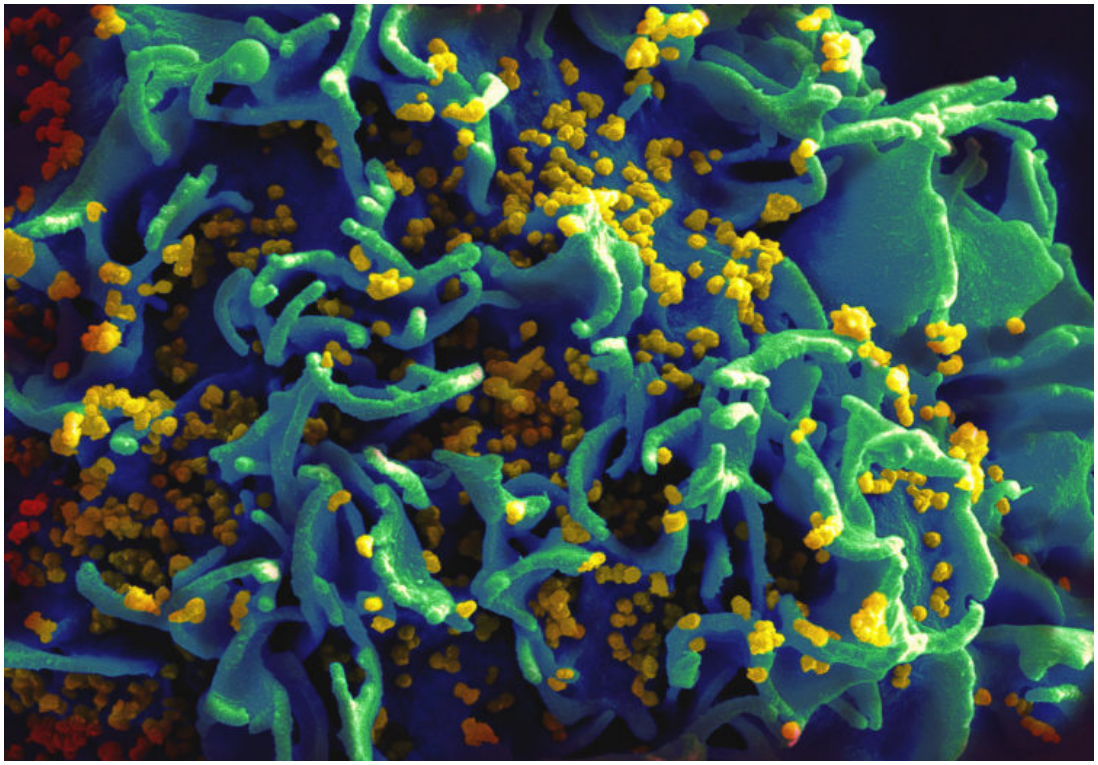
Secondary immunodeficiency can be defined as the occurrence of cellular or humoral immunodeficiency in an individual who had an intact immune system before the onset of the condition. These acquired forms of immunodeficiency result from a diverse number of environmental causes as a side effect of cytotoxic drugs, malignancy and malnutrition.



Malnutrition and Immunodeficiency

The most common cause of acquired immunodeficiency in the developing world is malnutrition.

Protein-calorie malnutrition is usually implicated in these cases. It can be categorized into two types, **Marasmus, and kwashiorkor. Marasmus** is characterized by protein deficiency along with deficient other nutrients in diet whereas **Kwashiorkor** is a protein deficiency disorder. Patients are clearly **underweight** and have **muscle wasting** in both conditions, but generalized **edema** is only encountered in kwashiorkor. Usually, patients develop a mixed picture.

Pathogenesis

The **thymus gland**, which is implicated in the production and maintenance of **T-cell immunity**, is atrophic in patients with severe malnutrition. Additionally, **thymic hormone production** is significantly reduced in these patients. As a consequence, **T-cell mediated delayed-type hypersensitivity reaction**, **lymphocyte proliferation**, and **CD4+ differentiated T-cells** are all reduced. While **immunoglobulins** are not affected in malnutrition-related immunodeficiency, **antigen processing by B-cells** is usually impaired due to the inability of antigen presentation by T-cells.

Neutrophils and other polymorphonuclear leucocytes also show impairments in malnourished patients. They show abnormal **phagocytosis** (inability for intracellular killing of engulfed organisms). **Natural killer cells** also show a decrease in function.

Malignancy and Immunodeficiency

Any form of malignancy can be associated with immunodeficiency in the end-stages of the disease. However, certain hematologic malignancies such as hemolytic anemia, leucopenia or thrombocytopenia are associated with early secondary immunodeficiency, and they should be studied in depth to understand the mechanisms of inducing immunodeficiency.

Lymphoid malignancies are known to be associated with acquired immunodeficiency and an increased risk of infections.

We will focus on three main types of lymphoid malignancies that are clearly associated with an increased risk of immunodeficiency:

- Lymphoma
- Leukemia
- Multiple myelomas

Lymphomas and Immunodeficiency

While **immunoglobulin deficiency** has been reported in **advanced non-Hodgkin lymphomas**, **Hodgkin lymphomas** are more commonly associated with impaired immunity. Hodgkin lymphoma can cause T-cell deficiency, depletion of T-cell precursors in lymphoid tissues and lymphopenia.

Additionally, patients with Hodgkin lymphoma show **impaired delayed-type hypersensitivity reactions** as a consequence of impaired T-cell responses to antigens. As a result of this, patients with Hodgkin lymphoma usually show lower rates of **allografts rejection**.

Similar to malnutrition, **immunoglobulins** are not reduced in Hodgkin lymphoma. In contrast to malnutrition induced immunodeficiency, patients with Hodgkin lymphoma show normal phagocytosis, and the **polymorphonuclear leucocytes** retain their ability for intracellular killing.

Non-Hodgkin Lymphoma induces impaired immunity due to continuous depletion of B cell and T cell.

Leukemia and Immunodeficiency

Patients with **leukemia** do not develop impaired T-cell or B-cell immune responses except for chronic lymphocytic leukemia.

Patients with chronic lymphocytic leukemia develop impaired B-cell immune responses due to the inability of B-cells to differentiate into plasma cells, which causes **hypogammaglobulinemia**. As a consequence, patients with chronic lymphocytic leukemia are unable to develop an immune response against **typhoid**, **diphtheria**, **tetanus**, **mumps**, **influenza** and **vibrio vaccines**.

Patients who have a **markedly low IgG level** are at highest risk of developing life-threatening infections. **Intravenous immunoglobulin treatment** is indicated in these patients to lower the risk of acquiring infections. Patients with chronic lymphocytic leukemia have a normal T-cell function with an impaired B-cell response.

Multiple Myeloma and Immunodeficiency

Patients with multiple myeloma develop impaired immunity due to the abundance of abnormal immunoglobulins. **Monoclonal immunoglobulins** in multiple myeloma are correlated with **hypogammaglobulinemia**. In addition to **impaired humoral immunity**, patients with multiple myeloma also have impaired antigen recognition and processing by B-cells. T-cell responses are usually intact in patients with multiple myeloma.

Infections and Immunodeficiency

Bacterial infections such as **mycobacterium leprae**, which causes leprosy, are associated with impaired T-cell immune responses. Patients might develop increased T-cell activity with low levels of mycobacterium leprae specific antibodies, or decreased T-cell activity with very high levels of antibodies against the bacterium.

Fungal infections such as **candidiasis** and **histoplasmosis** have been also associated with impaired delayed-type hypersensitivity reaction and the inability of lymphocytes to process antigens for poorly understood reasons.

Protozoal infections, especially with **malaria,** have been associated with impaired B-cell function secondary to impaired T-cell function. Such patients have a poor response to protein-based vaccines, such as tetanus and mumps vaccines.

Measles virus is associated with impaired T-cell and B-cell function, in addition to **lymphopenia**. The virus can also impair the function of natural killer cells. **The epstein-barr virus** is associated with impaired T-cell responses and **immunosuppression**. As a consequence, patients with **acute infectious mononucleosis** develop an impaired delayed hypersensitivity response and a reduction in the activity of natural killer cells.

Cytomegalovirus infects macrophages, which in turn play an important role in immunosuppression. Infected macrophages are rendered unable to present processed antigens for recognition by T-cells and B-cells.

Human Immunodeficiency Virus

Patients with HIV infection develop **lymphopenia**. In the acute stage is marked by an increase in **CD8+ T-cells** with progressive depletion of all T-cell and B-cell subtypes in later stages. **CD4+ T-cells** are usually more depleted than CD8+ T-cells, hence the **CD4+/CD8+ ratio** is usually lower than normal.

B-cells also show a wide myriad of abnormalities, which include poor response to new antigens, impaired antibody specific responses, and **polyclonal hyperimmunoglobulinemia**. HIV also causes impaired natural killer cells activity and the inability of antigen processing and presentation by macrophages.

Thus, above stated events marks the immunodeficiency acquired by HIV virus.

Drugs and Immunodeficiency

Corticosteroids are used for their anti-inflammatory action and their immunosuppressive properties. Corticosteroids affect immune responses by two different mechanisms: They **impact leukocyte traffic and leukocyte functions**. Corticosteroids also impact macrophages by limiting their ability to phagocyte and kill bacteria or other infecting organisms.

Glucocorticoids decrease the number of circulating CD4+ T-cells after the first injection by sequestration of T-cells into the lymphoid compartments. If no further injections are administered, the total CD4+ T-cells number should return to normal in two days.

In addition to their effect on T-cells function and traffic, glucocorticoids also affect interleukin production. IL-1, IL-2, IL-4 and IL-6 production are reduced after the administration of glucocorticoids.

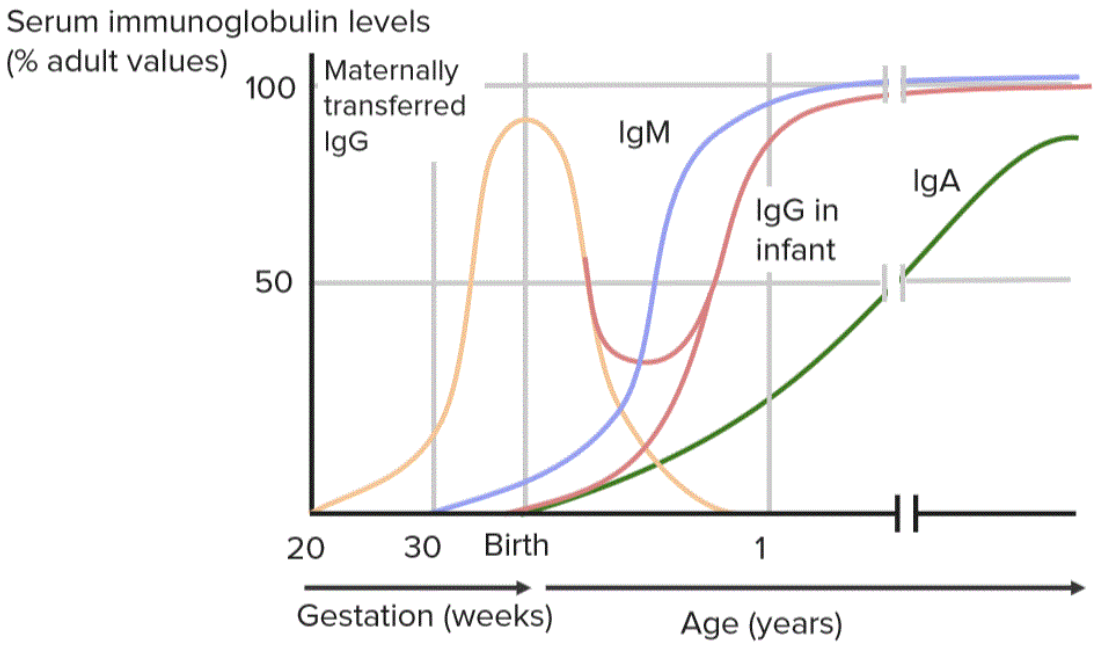
- **Cytotoxic agents** induce immunodeficiency by killing immune-related precursors. They, therefore, have an effect on all types of immune cells, including T-cells, B-cells, and macrophages.
- **Azathioprine** and its active metabolite, 6-mercaptopurine, inhibit **DNA synthesis** and arrest cells in the S-phase. They affect T-cells more than on B-cells. They do not impact the macrophages' function or numbers.
- **Cyclophosphamide**, another cytotoxic agent, inhibits DNA **replication,** and it is toxic to cells regardless of their cellular stage in the proliferation cycle. Cyclophosphamide is more toxic to B-cells but also has an effect on T-cells.
- Other drugs, such as cyclosporine and **anti-T cell monoclonal antibodies,** have been used in **organ transplantation** and are known to affect T-cell responses.

Premature Delivery and Immunodeficiency

Neonates who are delivered prematurely show impaired T-cell and B-cell responses, impaired antigen processing and presentation due to lack exposure to maternal immunoglobulins through placenta inside a womb. Additionally, full-term neonates are also largely dependent on **maternal IgA and IgG antibodies**, which cross via the placenta or breast milk which provide immunity to neonates against infections after birth.

Pregnancy and Immunodeficiency

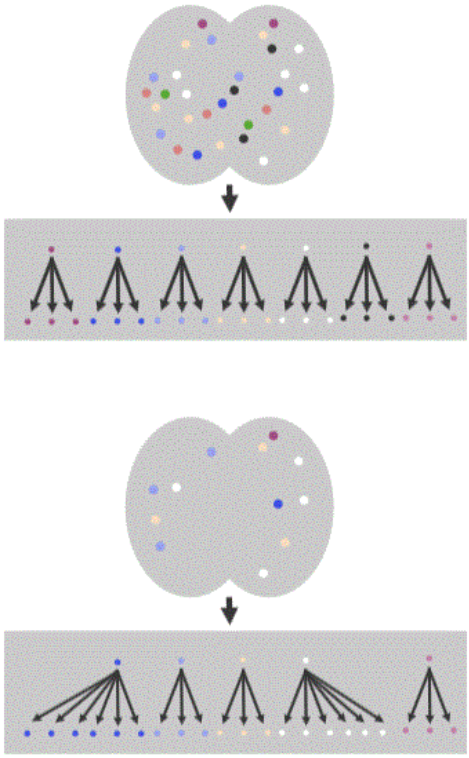
Pregnancy is a natural phenomenon that is associated with **physiologic immunosuppression**. Immunosuppression is specific to the **maternal-fetal interface** in the placenta. Pregnant women are at an increased risk of developing infections due to their impaired immunity.



"Serum Immunoglobulins in the Newborn" Image created by Lecturio

Aging and Immunodeficiency

Aging also affects the immune response, especially T-cells. The **thymus gland** decreases in size by 3% annually after puberty. As a result of this, response to infections and different vaccines decline in the elderly. Additionally, patients show impaired neutrophils, macrophages and natural killer cells activity leading to immune deficiency.



“Aging and Immunodeficiency” Image created by Lecturio

In infancy, the thymus produces T-cells with a mixture of specificities.

T-cell numbers in the peripheral pool are maintained by replication of circulating cells.

In early adult life, the thymus produces fewer T-cells.

In adult life, proliferation in the periphery maintains the size of the T-cell pool.

References

Gupta S. Immunodeficiency : Secondary. Encycl Life Sci 2001:1–6.

Notes