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Special Session 2

Relevant topics in immunopathology

Chairperson D Ferluga, *Slovenia* **Co-chairpersons:** C Nezelof, *France* and C Monteagudo *Spain*

Genetically determined primary immunodeficiencies: The role of thymic lesions in T-cell immunodeficiencies

C. Nezelof

La Facult~ de M6dicine de Paris, France.

The identification of inherited immunodeficiencies in humans has represented a major step forward in the basic knowledge of immunology. This is because: i) it supported the notion that the severity and recurrence of infectious diseases are not related to the intrinsic virulence of a given infectious agent but are directly related to the failure of the host to react with an appropriate response; ii) it facilitated the subsequent individualization of a recent, widespread and severe disease, AIDS; iii) it confirmed the dichotomy, already established in animals, between T- and B-cells and the corresponding cellular and humoral immunities; iv) it revealed, in a true experiment of nature, certain basic molecular mechanisms underlying the immune response as well as the pivotal role of primary lymphoid organs such as the thymus in the development of immunity (1); and v) it opened the way over a period of less than 30 years for appropriate and effective treatment of immunodeficient disorders (2).

Among the various immunodeficiencies, those involving cellular immunity and T-cell functions have been the latest to be individualized. Indeed, for a long time, the functions of the thymus were unknown and methods of evaluation of the T-cells, such as cytotoxic and proliferative tests, were not available (3). Within the yinphoid tissue, the thymus stands out as a very peculiar organ (1, 3, 4) because: i) it appears first during ontogeny; ii) it is provisional; iii) it functions mainly during fetal life and infancy; and iv) it is unique as a lymphoepithelial organ, made up of intimately admixed epithehal and self-renewing lymphoid elements.

The immunological role of the thymus has been established on the following basis: i) experimental data; ii) the identification of genetically immunodeficient animals; and iii) the discovery of special thymic abnormalities, such as agenesis and dysplasia in human immunodeficiencies.

Experimental data

From 1961 to 1962, J.F.A.P. Miller demonstrated that neonatal thymectomized mice consistently developed an immunodeficient state that preferentially affected cellular immunity and graft rejection. Comparatively, the ablation of the bursa of Fabricius in young chickens by B. Glick induced a failure to produce antibodies. These two works were of seminal importance and led R.A. Good to propose that the peripheral lymphoid system was made up of two components: T-derived cells and B-derived cells.

Genetically immunodeficient animals

Nude mice, moth-eaten mice and mice with severe combined immunodeficiency (SOID) are the commonest immunodeficient animals. They are used as recipients of human tumors. All these strains present not only poor peripheral lymphoid tissue but also a severely abnormal and underdeveloped thymic gland.

The fact that the genetic disorder involves both the differentiation of the skin and its appendages as well as the epithelial component of the thymus is indeed thought provoking.

Thymic abnormalities in human immunodeficiencies

Several thymic abnormalities have been found to be associated with human immune system deficiencies.

A genesis and ag/asia of the thvmus in DiGeorge syndrome

DiGeorge syndrome includes a dysmorphic fades with micrognathia, severe cardiovascular abnormalities and parathyroid hypoplasia. It is rarely complete (4). Often tiny fragments of the thymic gland can be discovered upon careful dissection of the neck. These fragments are made up of a histologically normal tissue (with Hassalian maturation), suggesting a quantitative deficit rather than a functional disorder of thymic activity.

DiGeorge syndrome results from an abnormal embryogenesis of the third and fourth pharyngeal pouch, frequently related to a partial monosomy of 22qllter. There is generally a close relationship between the severity of the cellular immunodeficiency and the amount of residual thymic tissue. The outcome is conditioned more by the severity of the hypocalcemia and the cardiovascular anomalies than by the degree of cellular immunodeficiency. However, cases of DiGeorge syndrome provided the object of the first attempts at restoring immunological competence by thymic grafts.

Thymic dysolasia in severe combined immunodeficiency

The term of thymic dysplasia applies to all the morphological abnormalities resulting from the embryologic maldevelopment of the thymus gland. Dysplastic thymuses are tiny in size, weigh less than 5 g and can be easily overlooked on dissection. Lymphoid cells are scarce or totally absent. The epithelial cells are present but, and this is the crucial feature, they fail to differentiate into a network and to form Hassal's corpuscles. They remain cohesive and form solid epithelial clumps (5, 6).

Whether this impairment in differentiation represents a primary disorder of the thymic epithelial tissue or a secondary phenomenon connected with a lack of migration of a bone-marrow-derived T-cell precursor is not known. In our experience, thymic dysplasia has never been found to be associated with normal T-cell functions

and, for this reason, can be regarded as the hallmark of inherited T-cell immunodeficiencies and more particularly SCID.

According to the severity of the impairment of the epithelial differentiation, three types of thymic dysplasias have been described (5): i) a pseudoglandular pattern, resembling acinar pancreatic tissue, representing the most primitive form. This type is frequently associated with a complete absence of lymph nodes and peripheral lymphoid tissue (except in the spleen); ii) a simple and common thymic dysplasia, characterized by separate lobules and clumps of cytokeratin-positive epithelial cells. Usually, these epithelial cells do not elaborate a clear-cut basement membrane. Capillaries, histiocytes, and some CD1-positive dendritic cells are present inside these epithelial clumps; iii) a thymic dysplasia with corticomedullary differentiation and pseudoatrophic pattern in which some lymphoid cells, either null or occasionally CD2- and CD68-positive, can be found. This pattern has to be distinguished from severe thymic atrophy, commonly observed in early severe malnutrition, chronic viral infection such as HIV, rubella and prolonged corticoid and cyclosporin treatment. Some differential morphological features are given in Table 1.

Table 1. Morphological differential featuree of thymic dysplasia and severe thymic atrophy.

	Thymic dysplasia	Severe thymic atrophy
Weightofthe gland	<5 g	>5g
Foliated architecture	Well preserved	Blurred
Interlobar tissue	Fatly	Fibroedipous with inflammatory cells
Size of the vessels	Small	Enlarged for the size of the lobules
Perivescular spaces	Empty	Fibrohyaline deposits
Epithelial maturation	Totally defective	Partially defective
Hassal's corpuscles	Absent	Absent or necrotic
Cytokeratin expression	Present	Often reduced
Lymphoid cells		
CD1	Absent	Absent
002	Absent or rare	Some present
004	Absent	Some present
CD8	Absent	Some present
Plasma cells	Absent	Present sometimes numerous
Thymic epithelial network	Maintained	Collapsed, disorganized

Although thymic dysplasia with corticomedullary differentiation and a pseudoatrophic pattern is more commonly observed in primary immunodeficiencies resulting from the accumulation of toxic metabolites due to enzymatic deficiencies such as adenosine deaminase deficiency or purine-nucleoside phosphorylase deficiency, the histological features of thymic dysplasias are not fixed and do not correlate well with any particular type of immunodeficiency (5, 6).

As said earlier, thymic dysplasia is a constant feature of SCID. Formerly called Swiss-type of agammaglobulinemia, SOID represents a collection of different genetic and immunological conditions, all obviously characterized by the absence of functional T-cells. Today, there is a consensus to distinguish between SCID with deficient T- and B-cells, and SOID with normal or high levels of B-cells (2, 7).

SC/fl with profoundlymohopenia affecting both T- and B-cells

This may result from: i) reticular dysgenesis, a highly unusual condition involving the coexistence of severe granulocytopenia with thrombocytopenia; ii) adenosine deaminase (ADA) deficiency (7), an enzymatic activity involved in the clearing of toxic metabolites. The ADA gene is mapped to 2Oql3ter; and iii) defects in two recombinase-activating genes (RAG-i and RAG-2), the product of which is required to make functional the rearrangement of immunoglobulin and T-cell receptors (7).

SCID with normal or high ievels of B-cells

This represents the largerst group. In most cases, the B-cells are increased in number but remain unable to differentiate into plasma cells and to elaborate immunoglobulins and specific antibodies. However, on some occasions, B-cells achieve complete plasma-cell maturation associated with normal quantitative and qualitative levels of immunoglobulins. This condition is commonly referred to as Nezelot's syndrome. Described as early as 1964, Nezelof syndrome, like DiGeorge syndrome, was of seminal importance since it provided the confirmation in humans of the dichotomy between the T- and B-cell systems already established in birds and mice.

Despite the presence of a normal structure in the peripheral yinphoid organs, that is, the presence of primary follicles (devoid of germinal centers) and plasma cells in lymphoid cords, patients with this syndrome are unable to produce specific antibodies (5, 7). Curiously, this impairment persists after successful bone-marrow transplant restoring T-cell immunity. The reason for this persistent failure of the B-cell system is not known. The patients have to be treated in the same manner as those with a hypogammaglobulinemia.

Apart from a few examples of purine nucleoside phosphorylase deficiency, most cases in this category are connected with mutations of genes encoding the common y-chain of the receptors for interleukins (ILs), IL-2, IL-4, IL-7, IL-9, and IL-is. The binding of IL-7 to its receptor has been demonstrated to be a crucial step in normal T-cell maturation (7). The gene encoding this y-chain is mapped to Xqi3 accounting for an X-linked transmission.

A mutation of a Janus kinase 3 (JAK3) gene, encoding a tyrosine kinase, has also been reported in some autosomal recessive forms affecting males and females. This genotype appears to be preferentially associated with Nezelof syndrome.

The cell deficiencies of the various forms of SCID usually also involve the CD56+ natural killer (NK) population. However, this absence of NK cells is not a constant feature and recent publications (2, 8) have emphasized the presence of NK cells at various levels in the peripheral blood of some patients. In a recent European survey, 50 out of 193 patients had NK±cells (8). The existence of NK activity has been reported both in SCID with and without B-cells. The presence of NK cells is probably not innocent. Indeed, it has been postulated that they could be implicated in some engraftment failures and delayed graft-versus-host disease in HLA haplo-incompatible bone marrow transplantation.

Conclusion

With their constant presence and the originality of their morphological expression, the thymic dysplastic lesions confirm in humans the close links between the capacity of differentiation of the thymic epithelial tissue and its ability to endorse immunological education of indigenous lymphoid cells. The mechanism underlying this func-

tion is unknown. The role of a hypothetical thymic hormone has not yet been documented, Intimate contact may be through emperipolesis between naive T-cells and the thymic epithelium and some dendritic cells, strongly expressing both class I and II antigens of the major histocompatibility complex, could represent a plausible alternative explanation. So far, no histochemical abnormality has been detected in the epithelial tissue, which expresses the usual 55-57 kd cytokerafin.

As could be anticipated, thymic graft has been proven to be successful in restoring T-cell function in these conditions. However, for technical reasons, bone marrow transplantation, or stem cells selected from umbilical blood has proven to be a more convenient and efficient procedure. This provides an adoptive immunity not only in SOID but also in DiGeorge syndrome (9).

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Opportunistic tumors associated with acquired immune deficiences

Hi. loachim

Dept. of Pathology, Lenox Hill Hospital, New York University and Columbia University, College of Physicians and Surgeons, New York, USA.

The immune system is a complex network of multiple specialized components able to potentiate, regulate, suppress and compensate each other under various conditions. Different components may malfunction or fail entirely due to congenital defects or acquired diseases. The result is an immune system that is functionally deficient. Organisms affected by immune deficiency are vulnerable to environmental agents, particularly to pathogenic microorganisms. Thus, infections with a wide spectrum of viruses, bacteria, fungi and protozoa, collectively referred to as opportunistic infections, may develop in immune deficient persons. They range from occult asymptomatic lesions to severe, and sometimes lethal, infectious diseases.

Immune deficient organisms are susceptible not only to infections, but also to neoplasms. The tumors arising in individuals with immune deficiencies, whether congenital or acquired, exhibit features similar to those characteristic of opportunistic infections. Like these, the tumors display increased aggressiveness and a tendency to early dissemination, resistance to treatment, frequent relapses and short survivals. To emphasize the analogy between causes and manifestations we refer to the immune deficiency-associated neoplasms as opportunistic tumors.

Two major categories of immune deficiencies are recognized: primary or congenital and secondary or acquired. The present discussion is focused on the neoplasms associated with acquired immune deficiencies. However, it should be noted that malignant tumors also occur with increased frequency in individuals with primary immune deficiencies. Children who survive the infections associated with various congenital immune deficiencies, such as X-linked agammaglobulinemia, Wiskott-Aldrich syndrome or ataxia telangiectasia, may be affected in up to 10% of cases by lymphomas, gliomas or other tumors. The general features of such neoplasms associated with congenital (primary) immune deficiencies are very similar to those occurring in persons with acquired (secondary) immune deficiencies.

Neoplasms associated with acquired immune deficiencies

Autoimmune diseases

The medical literature contains many reports of neoplasms, particularly those of the lymphoid system, occurring in patients with a history of Sjbgren's disease, rheumatoid arthritis, scleroderma, dermatomyositis, systemic lupus erythematosus and other autoimmune diseases. The increased risk of cancer may be related to the activation of lymphoid cells, excessive production of antibodies and deregulation of the immune system, all noted to occur in autoimmune diseases. Whether the deregulated immune system of autoimmune diseases represents a predisposition to malignancy or whether it simply renders organisms more susceptible to the oncogenic potential of therapeutic agents has not yet been determined.

Immunosuvoressive therany

The treatment of various types of cancers by ionizing radiation and cytotoxic drugs has become increasingly complex and efficient. Long-term disease-free survivals as well as complete cures are currently achieved in neoplasms that are uniformly fatal in the absence of treatment. This remarkable success in the treatment of cancer, however, has been accompanied by an increasing occurrence of new tumors in the longer surviving patients. Determining the respective roles played by carcinogenicity and immune deficiency in the origin of these tumors is difficult since both are adverse effects of chemotherapy and radiation treatments. Regardless of the mechanisms involved, a high incidence of malignancy associated with immunosuppression is well documented. The risk was greater for those treated in later years and this was apparently related to the introduction of combination as compared to single-drug chemotherapy. The features of high histological grade and extranodal location, particularly the brain and the gastrointestinal tract, are characteristic of lymphomas arising against a background of immune deficiency.

A remarkable phenomenon observed in relation to lymphomas induced by immunosuppression is their potential reversibility on