

Immunosuppression-Associated Pathology

Intact immunity is dependent on the interaction of a variety of immune cells and a multitude of secreted molecules. Hence, minor malfunctions in this complex system may substantially impact on the efficiency of the immune system, ultimately leading to the same result, namely increased susceptibility to infection and tumorigenesis. This special issue of *Pathobiology* on immunosuppression-associated pathology focuses on pathologies evolving from secondary immunodeficiency states induced by immunomodulatory drug therapy in the context of autoimmune diseases and in the prevention of transplant rejection.

Research on pathways and components that are more selectively interfering with the immune system has led to the emergence of a wealth of new immunomodulatory drugs. Their increased availability goes along with a widened clinical indication including various autoimmune diseases. In his overview, Kovarik delineates the most important principles of therapeutic immune modulations and their clinical indications as well as potential side effects.

In the past, histological investigations of tissues from patients treated with first-generation immunosuppressive drugs taught pathologists a different approach to this collective, as outlined beneath.

First, a spectrum of new categories of lymphoproliferative disorders, e.g. posttransplant lymphoproliferative disorder (PTLD) or other iatrogenic immunodeficiency-

associated lymphoproliferative disorders were observed and entered into the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.

Hussein et al. give a comprehensive overview on the pathogenesis of PTLD in general as well as focusing on a particular patient group, namely pediatric patients. The role of specific site involvement is underlined by the examples of the central nervous system and the skin, discussed in the papers by C. Kempf et al. and W. Kempf et al., respectively. W. Kempf et al. illustrate nicely how primary cutaneous PTLD differs in many aspects from its nodal and extranodal counterparts.

Second, lesions related to immunosuppressive drugs represent a paradigm of a close, reciprocal interconnection of the functionality of the immune system, viral replication and tumorigenesis. Lessons were learned. For example, on the one hand, that the reduction of immunosuppression leads to a regression of Epstein-Barr virus-induced lymphoproliferations and therefore chemotherapy upfront is maybe not necessary. On the other hand, accumulations of viral-induced cancers such as human papillomavirus-positive squamous cell carcinomas of the skin or Merkel cell polyomavirus in Merkel cell carcinoma and *human herpesvirus 8*-induced Kaposi sarcoma were more frequently observed in these patients, as shown by W. Kempf et al.

Third, we became aware of rare and thus far unknown viral-induced malignancies. Hussein et al. provide an

example of the poorly known Epstein-Barr virus-associated smooth muscle tumors in immunocompromised children.

Moreover, recently developed drugs like mycophenolate can mimic graft-versus-host disease or infectious colitis including cytomegalovirus infection, a distinction which is of utmost clinical importance but creates a challenging task, as Weber et al. describe in their article.

In summary, this special issue on immunosuppression-associated pathology aims at giving an overview of

little-known aspects in histopathological diagnosis in the context of secondary immunosuppression. Moreover, we present an up-to-date overview on currently available immunosuppressive treatment concepts and their potential diagnostic pitfalls. In particular, we hope to heighten the awareness of pathologists and clinicians to the fact that the management of immunosuppressed patients calls for an approach different from that of immunocompetent patients.

M. Tinguely