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## Immunodeficiency and its relation to lymphoid and other malignancies

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**Abstract** The reasons why immunodeficiency leads to malignant disorders are multifactorial. The overall incidence of malignancies in persons infected with the human deficiency virus (HIV) is estimated to be 40%. Other infecting agents, especially herpesvirus species, play a pivotal role in HIV-associated non-Hodgkin's lymphoma (NHL) and Kaposi's sarcoma (KS). Mucosa-associated lymphatic tissue (MALT) lymphoma in the stomach may be a result of a chronic gastritis caused by *Helicobacter pylori*, a gram-negative bacterium. The Epstein-Barr virus (EBV) genome can be found in a high percentage of lymphoma cells of HIV-NHL (nearly 100% in the primary lymphoma of the CNS and about 50% in all other lymphoma entities). In body-cavity based NHL, characterized by the absence of EBV and c-myc oncogenes, sequences of a herpesvirus were identified which corresponds to the gamma-herpes viremia found in KS. The Kaposi's sarcoma-associated herpesvirus (KSHV) was usually present in primary-effusion lymphoma (PEL). HIV-infection, which causes multiple dysfunctions within the immune system, triggers the cytokine dysregulation. An abnormal endogenous interferon (IFN)-alpha production is observed in HIV-infected patients with KS, especially in the later natural course of the disease. A monitoring of the IFN-system by MxA, a protein specifically induced by IFN's of type I, may be a necessary stratum of identifying patients who show superior effects and the greatest clinical benefit from treatment with IFN-alpha.

**Key words** Immunodeficiency · Malignant disorders · Cytokine dysregulation

### Introduction

Malignant disorders in immunodeficient patients are important models that help to understand the pathophysiology of malignancy, resulting in the development of new modes of treatment. Progression in this field is preconditioned by a profound knowledge of the involvement of pathogenetic factors, i.e., disrupted immunosurveillance, chronic antigen stimulation, cytokine dysregulation, viral infections, and the interaction of various oncogenes. The purpose of the recent symposium in Berlin, which was organized by D. Huhn, Virchow Clinic, Berlin, and H. Stein, University Clinic of Benjamin Franklin, Berlin, was to focus on these parameters with the aim of drawing conclusions for new therapeutic options.

### HIV-associated malignant lymphomas

*D. T. Scadden, Boston*, reported on data from larger clinical trials (Concorde study, ACTG 019 trial) concerning the coincidence of the acquired immune deficiency syndrome (AIDS) and cancer: 23% of all AIDS deaths have been cancer related, and the overall incidence of malignancies in persons infected with the human immunodeficiency virus (HIV) is estimated to be 40%.

The reasons why immunodeficiency leads to tumors are multifactorial. It may depend on inadequate defense against tumorigenic pathogens, insufficient tumor surveillance, and/or dysfunctional cytokine production.

In AIDS-related non-Hodgkin's lymphomas (AIDS-NHL) negative prognostic parameters are: age more than 35 years, intravenous drug abuse, low CD4(+) T-cell counts, and lymphoma stages III and IV. A complete response rate of 67% is achieved by a CHOP regime, of 54% with standard m-BACOP. Novel approaches to therapy are:

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- Conjugation of a modified ricin to a monoclonal antibody (anti-B4 which targets CD19) within a chemotherapy/immunotoxin schedule
- 5-Azacytidine for Epstein-Barr virus (EBV)-positive lymphoma, resulting in increased expression of latent EBV genes, which then might be targeted by cytotoxic T cells
- Administration of IL-2, which may lead to a shift of effector cell subpopulations
- Gene therapy, with EBV responsive promoters driving suicide genes

*D. Knowles, New York*, reported on 105 patients with NHL from the New York University Medical Center who were observed between 1981 and 1986 with 36 small noncleaved lymphomas (SNCC) of the Burkitt type and 25 large cell immunoblastic lymphomas; 29 of the patients proved to have AIDS-related lymphomas, all with B-cell phenotype. From the immunophenotypic characteristics arises a pathogenetic schedule of AIDS-NHL: Among polyclonal lymphomas, 37% contain EBV-positive clones and 20% contain mono- or oligoclonal B-cell populations, so that McGrath et al. classified them in 1991 as a new HIV-related disease process [1]. In SNCC c-myc oncogene activation is frequent.

In body-cavity based NHL, characterized by the absence of EBV and c-myc, Knowles identified sequences of herpesvirus which replicate in lymphoblastoid cells corresponding to the gamma-herpes viremia found in Kaposi's sarcoma. In pyothorax lymphoma (PAL) no evidence of Kaposi's sarcoma-associated herpesvirus (KSHV) was found, but it was usually present in primary-effusion lymphoma (PEL). In contrast to the Burkitt-type lymphoma, PEL is characterized by the presence of KSHV and the absence of c-myc. Based on the characteristics of 17 patients, Knowles classified PEL as a specific entity within the categories of AIDS-related NHL, with epidemic features similar to those of AIDS-KS. The patients have a poor prognosis and a very short survival.

*G. W. Bornkamm, Munich*, focused on the role of EBV in HIV-related lymphoma. There are two main categories of HIV-associated NHL, immunoblastic lymphoma (IL) and Burkitt's lymphoma (BL). The classification is often very difficult. C-myc is not found in IL of transplant recipients, and BL in AIDS frequently presents with features of IL and/or plasmocytic differentiation. The pathogenicity of EBV is expressed in the viral genome EBNA-2, a pleiotropic activator of membrane antigens. Membrane antigens such as CD22 and CD21 are located on a promoter (TP-1) which is responsible not only for initiation but also for maintenance of transformation. During a B-cell transformation by EBNA-2, c-myc transfected EBV-genes (ER/EB2-5) become independent of the oncogene, because they themselves express high levels of c-myc RNA. C-myc seriously impairs immune recognition, leading to a selection for immunologically unrecognizable BL cells. The BL phenotype can be regarded as a result of c-myc activation and loss of EBNA-2. It can be counteracted

by an increased expression of latent EBV genes, for instance by 5-azacytidine, which up-regulates ER/EBNA-2 in ER/EB2-5 cells.

*H.H. Herbst, Berlin*, suggested human herpesvirus type 6 (HHV-6) as a co-factor of AIDS-related lymphomas (ARL), which would include a triggering by the T-cell system.

Interleukin-10 (IL-10) as a Th2-type cytokine (elevated in parasitic disease with reduced Th1-cell function) proved to be an autocrine growth factor for EBV-(+) cell lines showing homologous features to an EBV gene product with BZLF1 (transactivation of lytic phase). The expression of EBER is also associated with an abnormal cytokine pattern resulting in high IL-10 levels.

*R. Weiss, Offenbach*, reported the results of the German multicenter trial for a risk-adapted treatment of HIV-associated lymphomas with CHOP as an induction therapy and a combination of zidovudine (ZDV) and interferon-alfa-2b (IFN-alfa-2b) maintenance treatment for the normal-risk group. Patients in the high-risk group received combination therapy with vincristine and prednisone. Of 158 patients, only 83 have been documented (due to CNS disease, other chemotherapy, final stage, etc.), and 75 have been treated according to protocol. In 38 patients of the normal-risk group dose intensity of IFN-alfa-2b was 70% of the calculated dosage over 1 year. There was one grade-3 skin toxicity due to IFN, mild reverse reactions, and bone marrow suppression as dose-limiting factors. Only one patient died of lymphoma within the IFN-alfa-2b/ZDV-group during maintenance therapy. The lymphocyte counts were stable during maintenance treatment and the survival was quite satisfactory, with a median of 634 days, so that it seems worthwhile to evaluate the clinical benefit of IFN-maintenance therapy in a randomized phase-III study.

*G. Przybylski, Philadelphia*, focused on the immunoglobulin gene analysis of EBV(-) AIDS lymphoma and found in the early stage of HIV infection the V gene pattern similar to that seen in peripheral blood lymphocytes of healthy individuals, while in the late phase a clonal deficit becomes more and more obvious. No investigation of EBV-(+) ARL has been done so far.

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### The interferon system and HIV-related malignancies

Improvements in therapeutic interventions for HIV infection as well as for the related malignancies will ultimately depend on a profound understanding of causes and effects of cytokine dysregulation within the natural course of these diseases. In the course of HIV infection the role of IFN-alfa seems to be rather paradoxical, as it can be viewed either as a therapeutic agent or as a major contributor to the pathology associated with AIDS. IFN-alfa is used as a standard treatment in certain stages of AIDS-associated Kaposi's sarcoma

(AIDS-KS) and experimentally in various complications which are related to AIDS or may occur concomitant with HIV infection (NHL, HIV-related immune thrombocytopenia, condyloma acuminata, hepatitis C, herpes simplex infections).

*Donna Mildvan, New York*, gave an overview of the endogenous IFN system and its clinical relevance. Immune activation and immune deficiency in HIV disease provide an intriguing interaction. An abnormal endogenous IFN-alpha production is observed in HIV patients, especially in the later natural course of the disease. The development of the wasting syndrome and AIDS dementia is cytokine mediated. The acid-labile endogenous IFN-alpha, which is probably derived from other IFN-producing cell subsets than usual, may be responsible for the induction of TNF-alpha. The endogenous IFN-alpha titers in HIV-infected patients can be down-regulated efficaciously by administering AZT [1].

Biological plausibility and practicability are preconditioned if cytokines may serve as surrogate markers in HIV disease. It is also necessary to elucidate the evidence that the cytokine network is involved in HIV disease and that treatment influences HIV-induced cytokines. A surrogate marker for the clinical activity of a drug has to reflect entirely the clinical benefit of the intervention.

*P. von Wussow, Hannover*, reported on the activation of the endogenous IFN system in HIV-infected persons and monitoring by measuring the MxA-protein levels. The interferons find receptors of various cells which produce their proteins. MxA-protein is specifically induced by IFNs of type I and shows a relatively long half-life of 5 days and a clear dose dependency on its inducer. Especially the long half-life preserves MxA a reliable marker compared with definitively shorter half-lives of IFN-alpha itself and the (2'-5'A)-oligoadenylatesynthetase as the corresponding enzyme.

While healthy persons as well as cancer patients show no expression of the MxA-protein, it is sensitively up-regulated in patients who are treated with IFN-alpha. In patients with AIDS and systemic lupus erythematosus (SLE) high endogenous titers of MxA are found to correlate with the course of disease measured in Walter Reed (WR) stages or in Centers for Disease Control (CDC) stages in HIV disease and by the disease activity index (DAI) in SLE. The results show ongoing IFN-alpha production as early as WR stage 2.

To elucidate the biological function of the MxA homologue the gene was transfected in mice cells and showed a suppression of infections within the animal model. The similarity of the endogenous IFN systems in HIV infection and SLE disease as hallmarks of a broad spectrum from autoimmune disease to immunodeficiency raises the question whether SLE is also induced by a – so far – unknown retrovirus or whether AIDS is something other than a retroviral disease.

*I. Schedel, Hannover*, reviewed therapy with IFN-alpha in HIV infection. At first glance, IFN-alpha seems

to be a model agent in HIV-related malignancies because it preserves all the properties which are desired in its antiretroviral, antiproliferative, and immunomodulatory modes of action.

As an antiretroviral agent it proved to reduce p24-antigen in a more than 75% [2] and by more than 93% in a combination with ZDV [3]. A clear evaluation of the clinical indications is still missing; the endogenous IFN-alpha system has been underestimated up to now as a necessary stratum identifying patients who show superior effects and the greatest clinical benefit from treatment with IFN-alpha.

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### **Kaposi's sarcoma – pathogenesis and clinical features**

The major unresolved issues in Kaposi's sarcoma (KS) are: the cell of origin, the question of whether the pathogenesis is neoplastic or reactive, and the etiologic agent. Knowles listed some candidates which are suspected of causing KS, such as cytomegalovirus (CMV), hepatitis-B virus (HBV), and KSHV, which was specified to a gamma-herpes viremia after identification of herpesvirus-like DNA and cloning of the differences between two complex genomes [4]. KSHV-DNA is encapsulated in herpes viral particles. They are infective and are able to transmit KSHV-DNA to cells. Foscarnet has been shown to be active against KSHV in some selected cases. KSHV is also found in up to 92% of non-AIDS-KS. It infects endothelial cells [5] and has been found to be associated with HHV-8 in peripheral blood in 52% of patients with KS and in 8% of persons without KS [6]. KS-associated herpesvirus-like DNA sequences are also present in a subset of ARL, exclusively in the body-cavity type [7]. Soulier et al. very recently published an association with Castleman's disease [8]. In five patients with localized disease they found no KSHV, while in three of four patients with multiantric disease the tests were positive.

*M. Stürzl, Munich*, gave a lecture about the role of cytokines in KS. KS appears from the beginning as multiple lesions with low mitosis rates. Cell interactions are presumed to occur between fibroblasts, monocytes, and the endothelial cells. As structural alterations of aortic endothelium are observed under the conditions of HIV infection, the involvement of other cell systems (such as the dendritic cell system) is highly probable. Besides structural alterations of tissue, there is an increased adhesion of leukocytes. In a cultivation of human dermal microvascular endothelial cells (HD-MVEC) an adhesion of monocytes of the U 837-lineage was stimulated by interleukin-1 $\beta$  (IL-1 $\beta$ ) and IFN-gamma.

KS can be regarded as a reactive process: infection of the monocytes with HIV and interaction of infected monocytes with endothelial cells, followed by expression of such specific growth factors as platelet-derived growth factor (PDGF) and transforming growth factor  $\beta$  (TGF- $\beta$ ), which leads to proliferating fibroblasts.

PDGF induces monocyte chemoattractant protein-1 (MCP-1), leading to macrophages and vascular endothelial growth factor (VEGF) showing synergy with basic fibroblast growth factor (bFGF) in the induction of angiogenic KS-like lesions in mice.

Is KS a malignancy or a dysregulation process? There is no primary lesion and no metastasis. It is polyclonal, so that it shows all features of a cytokine- and growth factor-mediated dysregulatory process.

*H. Rasokat, Cologne*, described the clinical features of KS and gave an overview of risk-related therapy. Primary KS appears as a sporadic, endemic, or epidemic feature; secondary KS is due to immunosuppressive medication, is AIDS related, or is caused by other immune deficiencies.

In AIDS-KS it is not wise to treat only KS; the HIV disease has to be considered as well. Regressions of disease under medical treatment have proven to be unstable without further medication. A significantly prolonged response (disease-free remission) was observed in patients receiving ZDV after a response to IFN-alpha compared with those who received no further therapy [9]. In advanced disease IFN-alpha is not the ideal medical intervention, because time to response is long (up to 12 weeks compared with 4 weeks in patients treated with a chemotherapy regime of ABV). IFN-alpha shows efficacy in disseminated KS when the immune state is satisfactory (CD4 counts higher than 200) with about 50% objective remissions. Combined with ZDV it can be administered in a lower dosage and with better results, even for patients with CD4 counts lower than 200. If the endogenous IFN-alpha production is considered for therapeutic strategies, Rasokat predicts an expanded indication, leading to a durable stabilization of the natural course of disease. A certain 'proof of the principle' has already been made by intervening early and treating for several years, as the results of *Mauss and Jablonowski* show [10].

### **Transplantation-related and *Helicobacter*-associated lymphoproliferative disorders**

In his lecture about transplantation-related lymphoma, Knowles gave the results of the histological classification and molecular gene rearrangement analysis of 22 patients with post-transplant lymphoproliferative disorders; 19 had had a previous heart transplant, two a transplant of kidneys, and one a lung transplantation. The median time from transplantation to diagnosis of lymphoproliferative disease was 11 months, with a wide range from 1.5 up to 96 months. In general, disease starts with a plasmocytic hyperplasia, going on to polymorphic B-cell hyperplasia and the development of B-cell lymphoma.

*H. Riess, Berlin*, characterized the clinical findings in secondary lymphoma, which may occur after transplantation of the heart, lung, or liver. Secondary lymphomas are usually B-NHL, whereas Hodgkin's disease, T-cell lymphoma, and multiple myeloma appear seldom.

EBV is involved in the pathogenesis of post-transplant B-NHL. Involvement of extranodal sites including CNS and the graft is frequent. CHOP as the standard chemotherapy may result in long-standing complete remissions.

*V. Daniel, Heidelberg*, reported on the results of G. Opelz et al. [12] from the Collaborative Transplantation Study group regarding the incidence of NHL in kidney and heart transplant recipients. Their risk of developing NHL is 20-(kidney) to 120-(heart) fold higher than that in the normal population, with a maximum increase in the first year after transplant. The recipient's age makes no difference after 1 year, but the incidence of lymphoma rises thereafter if the recipient is more than 50 years old. A donor origin of the disease is not yet clear, but it is suggested that it plays a major role only in bone marrow transplantation.

*V. Leblond, Paris*, reviewed treatment with anti-B-cell monoclonal antibodies in patients with post-transplant lymphoproliferative disorders; it was performed only from 1988 to 1992, being stopped in 1993 for economic reasons. The administered antibodies were ALB 9 (against CD24 antigen on B-cell line and granulocytes) and BL 13 (against CD21, EBV-receptor on B cells). Of ten patients, eight experienced a complete remission (CR) under antibody therapy, and seven are alive in CR. With standard chemotherapy 40% of patients with post-transplant lymphoproliferative disorders are cured.

*W. Siegert, Berlin*, reported on the occurrence of new malignancies in patients surviving more than 5 years after bone marrow transplantation (BMT). Data were collected by H. J. Kolb et al. from the Late Effect Study Group of the EBMT and EULEP [11]. New malignancies occurred in 47 patients, including neoplasms of the skin, oral cavity, uterine cervix, and breast, glioblastoma, lymphoma, and others. In multivariate analysis donor age above 30 years and chronic graft-versus-host disease were significant risk factors. Presumably, chronic immunosuppression is the pathogenetic basis, rather than the conditioning treatment prior to BMT.

*J. Lacerda, Lisbon*, reported his first results on immune cell transplantation in EBV-associated patients with LPD after allogeneic BMT. As the pathogenesis of LPD is dependent on immunosuppression characterized by deficient EBV-specific and HTLA-T-cell responses, an immune therapy with donor leukocytes is a possible cause of EBV-associated LPD in allogeneic BMT recipients. Of 14 patients with EBV-LPD (between 5 and 52 years old) after allogeneic BMT (five patients with AML, six with ALL, two with CML, and one with NHL) Lacerda found in all nine evaluable cases large IL-type B-cells of donor origin that generate large lymphomas in SCID mice. An adoptive immune therapy in the SCID mouse model was started which defined effector cells as anti-CD3. To define human effector cells, EBV monitoring by polymerase chain reaction (PCR) methods in peripheral blood is performed at St. Jude's Hospital in Memphis, TN.

P. Isaacson, London, gave an overview of the concept and the biology of the mucosa-associated lymphatic tissue (MALT) lymphomas. The MALT concept was invented by Isaacson, who was able to shed light on its special role in human lymphomas in recent years. MALT lymphomas are different from nodal lymphomas in that they do not arise primarily in lymph nodes but in lymphatic tissue associated with epithelial cells, e.g., stomach, lung, salivary glands. Clinical observation and now evolving molecular characterization clearly reveal a different phenotype of these lymphomas compared with nodal lymphomas. However, as in nodal lymphomas, low and high grades must be distinguished. Isaacson and Stolte, Bayreuth, showed that MALT lymphomas in the stomach may be the result of a chronic gastritis caused by *Helicobacter pylori*, a gram-negative bacterium. In addition Isaacson's group evaluated the role of different genetic lesions involved in the progression of this lymphoma entity. They looked for aberrations in the p53 tumor-suppressor gene, mismatch repair defects, and c-myc mutations. While p53-mutations were rarely detected in low-grade lymphomas, 20% of high grade MALT lymphomas harbored p53-mutations. This puts the p53-suppressor gene once again in the role of a major lesion involved in lymphoma progression. A. Neubauer, Berlin, reported that in his group of patients, Dr. Eidt of Cologne performed immunocytochemical studies and, as in Isaacson's group, detected p53-protein expression exclusively in high grade MALT lymphomas of the stomach, not in low-grade lymphomas. Isaacson also reported on lesions involving mismatch repair genes; his group showed that a replication error (RER) phenotype can be seen in many low- and high-grade lymphomas. Interestingly, he also detected an RER phenotype in some mucosal areas in patients without evidence of MALT lymphomas. Isaacson further presented data indicating that low-grade MALT lymphomas may be antigen driven; clinical data of six patients with low-grade MALT lymphomas showed that – following *Helicobacter pylori* eradication – a CR of their lymphoma had occurred.

These clinical data were extended by the German MALT-lymphoma trial headed by Stolte, Bayerdörffer, and Neubauer. Up to now, 74 patients with low-grade gastric MALT lymphomas and *Helicobacter* positive gastritis have been included. *Helicobacter* eradication was performed using omeprazole (120 mg daily × 14 days) and amoxicillin (2250 mg daily × 14 days); 63 (85%) of these 74 patients went into remission, 53 (72%) of them in complete histological and endoscopic remission. A caveat in this study are the 11 patients who did not enter remission; eight of these 11 were referred to surgery, and in six of these eight patients a high-grade MALT lymphoma was diagnosed from deeper mucosal areas. Thus, *Helicobacter* eradication as first-choice treatment for low-grade gastric MALT lymphomas should be performed only within clinical trials. Neubauer also presented molecular data indicating that most patients in CR after *Helicobacter* eradica-

tion are PCR-negative. His group further showed that mutations within the immunoglobulin heavy chain gene in the part encoding for the antigen-binding domain may be ongoing, similar to the data which had been presented by P. Isaacson. In summary, gastric MALT lymphomas may be seen as the result of a genetic multistep process in which infection with *Helicobacter pylori* plays a major role.

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