Some Immunological Aspects of Various Types of Specific Acquired Deficient Immune Status (SADIS) following Various Kinds of Microbial Infection - 3. the leukemia type .(Lk-type) of SADIS

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Like the Tb-type of SADIS, the leukemia-type (Lk-type) of SADIS may produce primary malignancies and unlike the Tb-type of SADIS, the Lk-type of SADIS may produce hematologic malignancies located in tissues of organs of the host.

The primary hematologic malignancies as disease expression of the Lk-type of SADIS are characterized by the existence of malignant proliferation of immuno-competent cells. Depending on location of the proliferating cells, the Lk-type of SADIS produces leukemia when malignant proliferation of cells takes place in blood, often also in bone marrow, and malignant lymphomas when malignant proliferation of cells occurs in lymphatic organs such as lymph nodes.

The diagnosis of hematologic malignancies can be based on cytologic examination of smear preparation obtained from blood or bone marrow and on histopathologic examination of biopsy tissue obtained from lymph nodes- or bone marrow[(1)]. The leukemias are characterized by the existence of neoplastic proliferation of one of the blood-forming cells[(2)] and of abnormal maturation and accumulation of white blood cells[(3)]. The different types of leukemia are classified according to the cell type involved and as acute or chronic depending on the duration of the disease[(2)].

Leukemias can be divided into the acute and chronic leukemias also on the basis of clinical and hematologic features. A block in maturation of lymphoid or granulocytic cells at the primitive blast stage is characteristic for the acute leukemias. These cells accumulate in bone marrow, peripheral blood and at times in other tissues[(3)]. Chronic leukemias are also disorders of maturation of cells resulting in accumulation of abnormal leukemic cells in bone marrow, lymph nodes, peripheral blood, liver, spleen and occasionally in other organs. These abnormal cells in chronic leukemias are better differentiated than are the abnormal cells in acute leukemias from morphological and functional points of view[(3)]. Chronic lymphocytic leukemias are characterized by the existence of progressive accumulation of small lymphocytes that have abnormally long lifespan in blood, lymph nodes, bone marrow, spleen and in other tissues[(3)]. The leukemic cells in chronic lymphocytic leukemia most often appear as small but otherwise normal lymphocytes which have low mitotic rates.

In about 95% of cases, the leukemic cells are B-lymphocytes and in the remainder these cells are T-lymphocytes[(3)]. There is evidence that abnormal cells in B-cell cases of leukemia derive from a single clone. Abnormalities of both B- and T-cell functions have been observed in patients suffering from chronic lymphocytic leukemia[(3)].

The human T-cell lymphotropic virus type I (HTLV-I) is the prototype of microbial pathogens that may produce the Lk-type of SADIS. This virus was discovered by the group led by Gallo at the National Cancer Institute in 1980. This human oncogenic RNA-virus which is also termed the adult T-cell leukemia virus is a member of the retroviruses (Scheffer 1984; quoted from Daenen S: Nederl. Tijdschr. v. Geneesk. 1984, 128, 957-960). This RNA-virus was isolated from lymphocytes of a patient that had a T-cell lymphoma located in the skin in 1980[(4)]. Retroviruses are characterized by the possession of the enzyme "reverse transcriptase". By means of this enzyme, a DNA copy can be produced from viral genome during the replication cycle which in this way can be integrated into the genome of the infected cell[s]. The oncogenic retroviruses are at present classified into the B-type, the C-type and the D-type. The C-type of viruses are the most important. These C-type of viruses are discovered as the causative agents for several kinds of leukemia, lymphomas and sarcomas in animals. The HTLV-I is a retrovirus of the C-type. (Scheffer 1984: quoted from Daenen S: NTvG 1984, 128, 957-960). There have been numerous reports on finding of type C virus particles as based on electron microscopic examination in

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plasma pellets or tissues obtained from patients suffering from leukemia[3].

Shortly after the discovery of HTLV-I in 1980 by Gallo et al., the adult T-cell leukemia virus (ATLV) was discovered in Japan in patients suffering from an endemic form of leukemia. This ATLV is now considered to be the same as or strongly related to the HTLV-I. Striking concentrations of ATLV are detected in some islands in south-west Japan (Scheffer 1984; quoted from Daenen S: NTvG 1984, 128, 957–960). Soon after the isolation of HTLV-I as the first retrovirus, a causal relationship can be established between the virus and an aggressive form of leukemia, the socalled "adult T-cell leukemia"[6]. Beside the adult T-cell leukemia, HTLV-I is associated with the development of the "tropical spastic paraparesis", which is a consequence of a progressive myelopathy caused by the virus[7]. The development of myelopathy has been described a few months following seroconversion[8]. The concomitant appearance of tropical spastic paraparesis and the adult T-cell leukemia in one patient is rare but has been described[9]. The incubation period is estimated to be 15–20 years[8].

Assuming that immune spectrum of individual cases of HTLV-I disease is (almost) identical to that of individual cases of tuberculosis, acute HTLV-I disease represents the L-type immune status, chronic form of HTLV-I disease the K-type immune status and the adult T-cell leukemia the KK-type immune status, which is termed the Lk-type of SADIS. (**fig. 1**).

Fig. 1 The Immune Spectrum of individual cases of HTLV-I disease

Immune status	**LL**	**L**	**K**	**KK**
Stage of disease:	acute HTLV-I disease	acute HTLV-I disease	chronic HTLV-I disease among others: tropical	Lk-type of SADIS adult T-cell leukemia
Disease express:		spastic paraparesis		

It is interesting to note that adult T-cell leukemia as disease expression of the Lk-type of SADIS is found in only 1–4% of HTLV-I infected individuals over their life time (Gallo; quoted from Asian Med. News, August 8, 1989). The risk to contract the disease following infection with HTLV-I is estimated to be about 4% when seroconversion has taken place before the age of 20 years". This implies that the greater part of HTLV-I infected individuals maintain their LL-type, their L-type or their K-type immune status over their life time and that a few may show progression of their K-type immune status to the Lk-type of SADIS, resulting in the development of the adilt T-cell leukemia. Contributory factors to this down-grading reaction in the immune spectrum of HTLV-I disease are reported to be ionizing radiation and some chemicals[7].

There are numerous reports on the finding of an increased incidence of acute non-lymphocytic leukemia in patients with non-neoplastic diseases that have been put under treatment with cytotoxic drugs especially alkylating agents[3]. The risk of contracting the acute non-lymphocytic leukemia appears to be greater with combined irradiation plus chemotherapy[3]. The above finding indicates also that progression of HTLV-I disease following primary infection to the development of the adult T-cell leukemia is a multistep process. Antibodies against HTLV-I are detected in various populations in seesawing rates. A relatively high seroprevalence was observed among others in many parts of Africa where seroprevalence is seesawing between 5–20%[11].

In approximately 100% of a group of Japanese patients suffering from the adult T-cell leukemia, antibodies against HTLV-I were found in serum°) and in 20–50% of their healthy relatives as well. Antibodies against various parts of the virus have, as can be expected, the same pattern of dissemination as the virus itself. In endemic areas in Japan, 30% of the adult population have antibodies against the virus (Scheffer 1984; quoted from Daenen S.: NTvG 1984, 128, 957–960).

Observations done to date indicate that HTLV is not a ubiquitary virus that is transmitted vertically through germ cells. It was reported that although the route of transmission is not clear, horizontal transmission of the disease to healthy subjects has to be considered possible. Intimate contact is needed for transmission, and direct cell to cell contact is crucial for the spread of the virus[12]. Transmission of HTLV-I takes place through sexual contact, by means of blood[13] and from mother to child[7]. It has to be noted that HTLV-I has been isolated in patients from cell culture of mononuclear cells from blood and from cerebrospinal fluid[14].

It is interesting to note that HTLV-I can be detected only in T-cells, Neither the virus nor its RNA or proviral RNA has been detected in the B-cells (Scheffer 1984; quoted from Daenen S.: NTvG 1984, 128, 957–960). There is long period of latency of the disease. Being infected doesn't necessarily mean that a malignant lymphoma will develop[15].

Patients with the adult T-cell leukemia from Japan[16] and the West Indies[17] had similar disease expression but almost all had lymphadenopathy. There were often several patients found in one family suffering from the adult T-cell leukemia[16]. Patients dually infected with the human immunodeficiency virus type 1 (HIV-1), formerly designated the human T-cell lymphotropic virus type III (HTLV-III), and HTLV-I tend to develop frank AIDS more rapidly (Gallo; quoted from Asian Med. News, August 8, 1989).

A few years following the discovery of HTLV-I by Robert Gallo in 1980, a related virus was isolated from a patient suffering from the "hairy cell leukemia", designated the human T-cell lymphotropic virus type II (HTLV-II)[18]. The pathway through which the HTLV-II produce the Lk-type of SADIS is supposed to be similar to that of HTLV-I **(fig. 2).**

Hairy cell leukemia also termed leukemic reticuloendotheliosis is a chronic leukemia. This RNA-virus affects mainly older adult males with presenting symptoms such as fatigue, malaise, pancytopenia, splenomegaly and at times lymphadenopathy[3]. Pathologic findings are mainly found in bone marrow,

Fig. 2 The Immune Spectrum of individual cases of HTLV-II disease

Immune status	LL	L	K	KK
Stage of disease:	acute HTLV-II disease	acute HTLV-II disease	chronic HTLV-11 disease	Lk-type of SADIS hairy cell leukemia
Disease express:				

liver, spleen and peripheral blood. Abnormal cells are found in peripheral blood. Light microscopic examination reveals the presence of irregular fingerlike projections of cytoplasm from which the term hairy cell leukemia originates. These findings are confirmed by electron microscopy[3].

Disease expression of the Lk-type of SADIS other than leukemia, is the malignant lymphoma. The prototype of microbial pathogen that may produce the Lk-type of SADIS that gives rise to the development of malignant lymphoma is the Epstein-Barr virus (EBV) **(fig** 3). Like the adult T-cell leukemia and the hairy cell leukemia, the malignant lymphomas brought about by EBV are primary hematologic malignancies which means that EBV is the causative microbial pathogen of the mentioned malignancy. Primary infection with EBV results in the development of acute mononucleosis infectiosa, which may occur at any age. The vast majority of population are infected with this EBV during childhood or adolescence. This EBV-infection often doesn't produce any symptoms, but in approximately 50% of adolescents and young adults, infection with the virus gives rise to the development of infectious mononucleosis, also known as the disease of Pfeiffer[17]. This virus infects preferably the B-lymphocytes. Like other herpes viruses, this EBV shows lifelong persistence in EBV-infected individuals, particularly in the B-cells, the glandula parotis and the nasopharynx[19].

Fig. 3 The Immune Spectrum of individual cases of EBV-disease

Immune status	LL	L	K	KK
Stage of disease:	acute *EBV*-disease	acute *EBV*-disease	chronic *EBV*-disease	Lk-type of SADIS
Disease express:	acute mononucleosis infect.	acute mononucleosis infect.	chronic mononucleosis infect.	NHL* HD**

Note :
** NHL = Non-Hodgkin lymphoma*
*** HD = Hodgkin's disease*

Acute infectious mononucleosis has fever, headache, pharyngitis, generalized lymphadenopathy, splenomegaly, myalgia and articular swelling as characteristic symptoms and signs[16]. Peripheral blood examination reveals the existence of absolute T-celland B-cell lymphocytosis. Atypical lymphocytes are found up to 56% in peripheral blood[16]. Mononucleosis is a name derived from the atypical mononuclear cells in blood like those which were described for the first time by Downey and McKintey[20]. These cells are especially related to a primary infection with EBV, although they are also found in cytomegalo virus disease, influenza B disease[21]. Beside the lymphocytosis, neutropenia is found in approximately two third of patients suffering from mononucleosis infectiosa[22]. Superinfection in mononucleosis infectiosa could be accounted for by the neutropenia together with T-cell suppression[22]. Oedema of the eyelids plus painful swollen fingers which might be observed during the early stage of the disease are unusual manifestation of mononucleosis infectiosa[23].

Histologic examination reveals the presence of marked lymphoproliferation in almost all lymphoid tissues which is secondary to the entry of EBV into B-cells. This induces a short-lived increase in B-lymphocytes which is followed by a marked and prolonged T-lymphocyte response[3].

Elevation of soluble CD25 (sCD25) levels are used to assess the degree of lymphocyte activation in patients[24]. Stimulation of T-lymphocytes in vitro gives rise to a rapid increase in CD25 membrane expression[24]. Nelson and coworkers showed in 1985 that in vitro activated T-lymphocytes also produce a soluble form of CD25[25]. Soluble CD25 is the soluble fragment of Interleukin-2 receptor also known as the soluble membrane receptor. It can be shown by means of ELISA that the in vitro production of sCD25 is a reflection of the degree of T-cell activation[24]. In serum of patients with infectious mononucleosis elevated soluble CD25 levels are encountered[26]. In serum of healthy individuals, low levels of sCD25 can be found which are considered products of a normally functioning immune system. The normal values of sCD25 are in a rather narrow range of 325-405 U/ml[24]. Macrophages and B-lymphocytes produce sCD25 only in small amounts in vitro[24] .

In patients with the adult T-cell leukemia, the hairy cell leukemia and the non-Hodgkin lymphoma, there is a strong CD25 expression on the cell membrane and the molecule is continuously excreted in large amounts[27]. Serum levels up to 15000 U/mI have been reported[24].

There is decreased delayed skin hypersensitivity to antigens during the acute phase of mononucleosis infectiosa[3]. Recent studies suggest that the T-cell lymphocytosis which is found in response to primary EBV-infection of B-cells is a suppressor T-cell response thereby limiting the proliferation of B-cells and possibly preventing the development of malignant transformation[3].

Following infection with EBV, antibodies of the IgG and the IgM classes are produced against the viral capside antigen (EBVCA)[16]. The presence of IgM antibodies against the capside antigen ofEBV indicates that primary infection with the virus has taken place[21]. The 1gM antibodies disappear following primary infection; IgG antibodies on the other hand, show lifelong persistence[16] . Antibodies against the early antigen complex (EBVEA) are also found following infection with EBV. This early antigen complex consists of proteins which are synthesized by the virus during primary infection[16]. Most interesting to note is the persistent presence of antibodies against EBVEA, often in high titers. Positive EBVEA titers are found in patients who have the Burkitt lymphoma and some forms of nasopharynx carcinoma. Also in healthy individuals, positive titers of EBVEA can be

observed in periods of decreased immunoprotective capacity, such as in the elderly, during pregnancy or during the advent of immunosuppressive agents[20]. Antibodies against the nuclear antigen (EBVNA) are synthesized late following primary infection. These antibodies are produced in the nucleus of EBV-infected B-lymphocytes and remain lifelong in the body of the hose[16].

The diagnosis of mononucleosis infectiosa is confirmed by the presence of striking lymphocytosis with atypical lymphocytes as a rule, the presence of specific heterophyl antibodies (reaction of Paul Bunnell) and the presence of specific antibodies against the viral antigens (EBVCA, EBVEA, EBVNA)[28].

In general, spontaneous recovery from EBV-disease has been observed in the vast majority of patients suffering from primary mononucleosis infectiosa. In a few however, symptoms of primary EBV-disease may persist for several months to several years. Members of families with the recessive immunodeficiency syndrome, the Duncan syndrome which is an x-linked immunodeficiency syndrome, die due to overwhelming infection during the acute stage of mononucleosis infectiosa, or they get agammaglobulinemia subsequently, or malignant lymphoma many years later[29].

Multiple and repeated endogenic and/or exogenic reinfections with EBV following primary acute EBV-disease, may give rise to the development of a downgrading reaction in the immune spectrum of the disease, resulting in the progression from the L-type to the K-type and further to the KK-type immune status which may be either the Tb-type or the Lk-type of SADIS. It is int[r]iguing to speculate that when smoking is the contributory factor for immune status of chronic EBV-disease to progress to the Tb-type of SADIS, ionizing radiation and some chemicals are the potential contributory factors for immune status of chronic EBV-disease to progress to the Lk-type of SADIS. Disease expression of the Tb-type of SADIS due to EBV is the epithelial malignancy known as the nasopharynx carcinoma and that of the Lk-type of SADIS due to EBV is the lymphoid malignancy which may be either the non-Hodgkin lymphoma (NHL) or the Hodgkin's disease (HD). Chemotherapy using cyclosporine may in the long run lead to the development of malignancies due to aspecific immunosuppression[30]. Of the 661 patients with nephrotic syndrome under treatment with cyclosporine, five were found to contract malignancy[31]. Of the five patients that contracted malignancy following- prolonged treatment with cyclosporine for nephrotic syndrome, two had the Hodgkin's disease and three had carcinoma[31].

Lymphoid malignancy or lymphoma malignum is a malignant disease of the lymphoid .system which comprises the non-Hodgkin lymphoma, the Hodgkin's disease and the multiple myeloma. The adult T-cell leukemia is a variant of the lymphoma malignum[15]. Non-Hodgkin lumphoma is defined as autonomously growing and clonal proliferation of lymphocytes[32]. The NHLs are a heterogeneous group of malignancies which primarily involve lymphoid tissue. Relation between EBV and the malignant lymphoma was established[15]. It appears that there is an association between a form of NHL in Africa, the Burkitt lymphoma and evidence of infection with EBV[33]. There is high incidence of antobodies to EBV antigens especially the EBV early antigen (EBVEA) in Burkitt lymphoma[3]. Positive EBVEA titers are also found in patients suffering from some forms of nasopharynx carcinoma[20].

There are NHLs of the B-cell as well as of the T-cell type. The greater part of NHLs are of the B-cell type[33] and that most of the B-cell lymphoma derive from lymphocytes which are present in the follicle centre of the cortex of lymph nodes[34]. Non-Hodgkin lymphomas are reflections of the stages of differentiation of T- and of B-cells[35,36]. The prognosis of T-cell lymphomas is in general poorer than that of B-cell lymphomas[34].

In order to know whether NHL is of B-cell or of T-cell type, immunophenotyping has to be carried out beside the histopathologic examination of the malignancy[21]. Phenotyping of tumors of the lymphatic system is based on the insight that they consist pretty much of uninhibited growing cells which belong to one clone (monoclonal proliferation), that cells of this clone are almost all in the same stage of maturation (differentiation arrest) and that this stage can be located somewhere in the normal development of the lymphatic system[1].

It is sometimes difficult to differentiate between a reactive process and a malignancy based on histopathologic abnormality in lymph node follicles. Tumors are (almost always) monoclonal and the existence of a monoclonal pattern is of direct diagnostic value[1]. There are nodal and extranodal locations of NHL, i.e. in central nervous system and the gastro-intestinal tract[33]. Approximately 40% of NHLs are located extranodally[37]. The median survival is best for patients with B-cell lymphoma, less for patients with T-cell lymphoma and least for patients with non-T-non-B- cell lymphoma[38]. The Burkitt lymphoma is a B-cell lymphoma[3]. There is strong expression of CD25 on cell membrane in patients with NHL; this molecule is continuously excreted in great numbers[27]. Serum levels of sCD25 is a reflection of the total tumor mass and that serum levels decrease to normal values following successful cytostatic therapy[24].

Hodgkin's disease (HD) is a lymphoproliferative disorder which means there is neoplas tic proliferation in lymph nodes[39]. The cause of HD is unknown, but a number of features point to a viral aetiology perhaps with altered protective immunity. At present, the most likely causative agent appears to be the Epstein-Barr virus[39]. The disease is characterized histopathologically by the presence of the Reed-Sternberg cells. It is generally accepted that the malignant cell is the Reed-Sternberg cell[39]. The origin of the Reed-Sternberg cell and its mononuclear variants remains controversial. Different investigators have presented evidence implicating the T- and the B-cell and the macrophage-monocyte as the cell of origin in Hodgkin's disease. Current evidence favours the macrophage-monocyte as the primary malignant cell([3]). Cabanillas et al. suggested that the malignant cell of HD is a B-cell([40]). The Reed-Sternberg cell is also reported to be lymphocytic in origin and may be of T-cell or of B-cell phenotype[39].

Lymphocyte predominance which may be diffuse or nodular, is encountered in about 10% of cases of Hodgkin's disease.

The nodular form of HD has now been shown to be a B-cell lymphoproliferative disease. Depletion of lymphocytes is comparatively rare in Hodgkin's disease[39]. Lymphocyte predominance type is encountered in younger patients, is usually limited in extent and has an excellent prognosis. Most investigators believe that the lymphocytic infiltrate found in histopathologic lesions of HID represents host cellular immune response against the tumor and correlation with a favourable prognosis. Patients with lymphocytic predominance therefore have a strong host immune response against the tumor[3].

Lymphocyte depletion type is at the opposite end of the spectrum of HD, usually presenting with widespread disease and constitutional symptoms and having a poor prognosis. Patients with the lymphocyte depletion type of HD show a failure of response of the immune system to the tumor[3].

In the spectrum of chronic infectious diseases which may progress to SADIS, the lymphocyte depletion type of HD is located nearer to the leprosy-type of SADIS than to the tuberculosis-type of SADIS. (**fig. 4**). Defects in cell-mediated immunity are found in HD which can be demonstrated by doing skin testing and in vitro transformation testing in response to mitogens and antigens[3].

Fig. 4 The spectrum of various types of SADIS

Microbial pathogen	Type of SADIS	Disease expression	Lympho-cytes
– M. tuberc. Helicob. pylori	Tb-type	epithelial carcinoma	predominance
– EBV, HBV, HCV, HPV, HSV	Tb-type	epithelial carcinoma	predominance
– HTLV-I, HTLV-U	Lk-type	leukemia	predominance
– EBV	Lk-type	NHL* Hodgkin's dis.:	predominance predominance
– HTLV-III(HIV-1)	Lp-type	AIDS**	depletion
– M. leprae	Lp-type	LL-type leprosy	depletion

** NHL = Non-Hodgkin Lymphoma*
*** AIDS = Acquired Immuno Deficiency Syndrome*

It is important to note that patients must be tested before chemotherapy and radiotherapy which are themselves immunosuppressive[3], especially when dealing with patients suffering from HD of the lymphocyte depletion type. The defect in advanced HD includes a disproportionate excess of suppressor lymphocytes despite tje existence of overall lymphocyte depletion with frequent lymphopenia[3].

As was postulated by Boveri in 1914, transition of normal to malignant proliferation of cells is brought about by chromosome aberrations[41]. There are a lot of correlations between specific chromosome abnormalities and disease characteristics in the NHL and the disease of Hodgkin[42]. It can be assumed that aberrations found in both the disease of Hodgkin and the non-Hodgkin lumphoma play a role in the emergence of unregulated growth in general and that aberrations found in either one of the above diseases play a role in the development of the ultimate phenotype of the disease, either in the direction of NHL or in the direction of the disease of Hodgkin[42]. The chances of survival of HD are much better than that of non-Hodgkin lymphoma[34].

Disease expression of the Lk-type of SADIS is the primary hematologic malignancy located in tissues of organs of the host. The development of primary hematologic malignancy is based on the existence of malignant proliferation of immunocompetent cells. Like in the solid malignancy as disease expression of the Tb-type of S ADIS which has lymphocyte predominance, entrapment of microbial pathogens in the histopathologic lesions of the malignancy likely occurs in the primary hematologic malignancies which makes the disease not any more infectious except probably in the lymphocyte depletion tupe of Hodgkin's disease.

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Proper words in proper places make the true definition of a style