Hematopoietic Stem Cell Transplantation and Other Management Strategies for MHC Class II Deficiency

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Major histocompatibility complex (MHC) class II expression deficiency is a rare condition that results in primary immunodeficiency (MIM 209920). It is inherited as an autosomal recessive trait.[1] This disorder was first identified in 1978.[2] It is also frequently referred to as the (BLS). However, the term "bare lymphocyte syndrome" was first used to describe a defect in MHC class I expression in patients[3] and has been used synonymously for all defects involving expression of MHC class I (BLS type I), MHC class II (BLS type II), or both (BLS type III).[4] This article focuses only on the disorder that is associated with a defect in MHC class II expression and thus uses the term MHC class II deficiency. A deficiency in MHC class II expression leads to impaired antigen presentation by HLA-DR, HLA-DP, and HLA-DQ molecules on antigen-presenting cells (APCs), such as dendritic cells and macrophages.[5] This leads to combined immunodeficiency with defective CD4^{+} T-cell development and a lack of T helper cell–dependent antibody production by B cells. MHC class II deficiency can be diagnosed by studying the cellular expression of MHC class II molecules, HLA-DR, on lymphocytes and monocytes. Patients with this disorder have no or a very low

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level of MHC class II molecules detected on their B cells and monocytes. As for other combined immunodeficiency disorders, hematopoietic stem cell transplantation (HSCT) is currently the only available curative treatment for MHC class II deficiency.

MHC CLASS II EXPRESSION DEFICIENCY AND GENETICS

The MHC locus itself is intact in patients with MHC class II expression deficiency. The lack of expression of DR, DQ, and DP MHC class II proteins on APCs is a result of impaired transcription of the MHC class II genes.[2] Previous somatic fusion experiments identified 4 complementation groups (A, B, C, and D).[6] Four disease-causing genes have since been identified and shown to encode regulatory factors controlling the transcription of MHC class II genes: CIITA for group A (MIM 600005),[7] RFXANK for group B (MIM 603200),[8] RFX5 for group C (MIM 601863),[9] and RFXAP for group D (MIM 601861).[10,11] The RFXANK, RFX5, and RFXAP proteins are all subunits of the ubiquitously expressed RFX complex. This complex binds directly to the promoters of all MHC class II genes and, together with other pleiotropic factors, forms the MHC class II enhanceosome. CIITA is an inducible factor that controls the expression of MHC class II genes expression by binding to the RFX complex and triggering transcription.

MHC CLASS II EXPRESSION DEFICIENCY, CLINICAL MANIFESTATIONS, AND OUTCOME

More than 100 unrelated patients have been reported worldwide. Most patients are of North African origin (Algeria, Tunisia, and Morocco)[2,12,13] (Picard, unpublished data, 2010). Other patients have diverse ethnic backgrounds, including Israel, the Kingdom of Saudi Arabia, Pakistan, Turkey, France, Holland, Italy, Spain, and the United States of America.[2,12,14–16] Half of the reported cases have RFXANK deficiency (they belong to the complementation group B),[2] 75% of which are of North African descent (Morocco, Algeria, and Tunisia). A 26–base pair deletion disrupting a splice site has been found in 32 unrelated North African patients, indicating the existence of a founder effect[16] (Picard, unpublished data, 2010). The clinical course of disease, which is identical in the 4 groups, is characterized by the recurrence of bacterial, viral, fungal, and protozoan infections. Severe and chronic viral infections (eg, cytomegalovirus, herpes simplex virus, adenovirus, and enterovirus) are the hallmarks of this immunodeficiency and are associated with a poor prognosis. Recurrent bronchopulmonary infections caused by bacteria, viruses, and *Pneumocystis jiroveci* are particularly frequent. Protracted diarrhea, often leading to growth failure and severe hepatobiliary disease, is also common. Patients may also develop progressive hepatic failure caused by *cryptosporidium* infection. Infections start within the first year of life, and subsequent evolution of the disease is characterized by an inexorable progression of infectious complications until death ensues. Although some children reach puberty, and a few survive into adulthood, the majority die before the age of 10 years.

MHC CLASS II EXPRESSION DEFICIENCY AND IMMUNOLOGIC FEATURES

The immunologic characteristics of MHC class II deficiency can be accounted for by the absence of antigen presentation via MHC class II molecules. Patients are unable to mount $CD4^+$ T-cell–mediated immune responses to specific antigens. Consistent with this, patient T cells do not show an in vitro response to antigens, which the patients had been immunized with or sensitized to by infection. Patients display T-cell lymphopenia, with a low $CD4^+$ T-cell count but a $CD8^+$ T-cell count that may be normal or low. The reduced number of $CD4^+$ T cells reflects the abnormal development of

CD4$^+$ thymocytes, resulting from defective MHC class II expression in the thymus. Surprisingly, however, the remaining CD4$^+$ T-cell population seems to be phenotypically and functionally normal.[17] Patient's CD4$^+$ T cells show normal alloreactive and proliferative responses to mitogens, but their potential function for physiologic responses are not known.[2] Although numbers of circulating B lymphocytes are normal, humoral immunity is severely impaired. Most patients have hypogammaglobulinemia, some with a reduced level of 1 or 2 immunoglobulin (Ig) isotypes, whereas some patients exhibit a hyper IgM profile. Patients do not show antibody responses to immunization and infection by microbial agents, except for a T-cell–independent antibody response against encapsulated bacteria. Autoantibodies associated with autoimmune disorders have been found in several patients. In conclusion, most patients are severely immunodeficient, with a low CD4$^+$ T-cell count and profound impairment of antigen-specific T- and B-cell responses.[2]

MHC CLASS II EXPRESSION DEFICIENCY AND SUPPORTIVE TREATMENT

MHC class II deficiency has a poor prognosis, with a life expectancy of only a few years.[2,13] Only a minority of patients, characterized by a less severe clinical course, survives beyond the age of 20 years. There are no clear differences in prognosis among patients belonging to the 4 different genetic complementation groups. The leaky immunologic phenotype of some atypical patients is associated with a better outcome.[2] Treatment of infections and other complications can at best reduce the frequency and severity of the clinical problems that are associated with MHC class II deficiency. The optimal symptomatic care available to date involves the prophylactic use of antibiotics and administration of Ig with adequate nutritional support. Patients receive substitutive subcutaneous or intravenous Ig therapy (0.4 g/kg by 3 weeks). Regular Ig substitutive therapy results in a marked decrease in the number of bacterial infectious episodes. Patients also require antipneumocystis prophylaxis (trimethoprim-sulfamethoxazole, 25 mg/kg, 3 times a week). All live vaccines are strictly contraindicated in patients with MCH class II deficiency. A few patients have developed chronic lymphocytic meningitis caused by live attenuated poliovirus vaccination.[13] Finally, every effort should be made to detect viral replication in MHC class II–deficient patients who are candidates for HSCT (see later discussion).[18]

MHC CLASS II EXPRESSION DEFICIENCY AND HSCT

HSCT is the only known treatment available to cure MHC class II expression deficiency. HSCT indication depends on clinical status (age, whether the patient is free from infection) and the availability of an HLA-compatible stem cell transplant donor.[18–20] Successful outcomes have been described, with narrow follow-up extending to more than 28 years.[18–20] European Registry data show that the survival rate associated with HSCT in patients with MHC class II deficiency is lower than that in patients with other forms of primary immunodeficiency.[18,20,21] This observation is independent of whether matched or nonmatched donors are used. HLA nonidentical transplantation (haploidentical or mismatched donors) for MHC class II immunodeficiency seems to be associated with a poor prognosis, with previous findings showing only 32% of patients to survive for more than one year after transplantation,[20] whereas 53% of patients receiving HLA-identical transplantation survived for more than one year.[18] A higher success rate seems to be achieved in patients undergoing HSCT before the age of 2 years.[19]

Moreover, MHC class II–deficient patients undergoing HSCT have increased risk to develop graft-versus-host disease (GvHD). Indeed, in the authors' experience among

15 patients with MHC class II deficiency, who had received transplants from an HLA-identical donor, the acute GvHD rate was 73%.[18] This rate was higher than GvHD rates reported for HSCT in patients with other primary immunodeficiency disorders.[20] The incidence and severity of GvHD seems to be correlated with the presence of ongoing viral infection before HSCT.[18] Aggressive antiinfectious therapy before HSCT, such as preemptive therapy against viral infections involving adenovirus, cytomegalovirus, or enterovirus, may therefore be beneficial in such patients. In conclusion, HSCT should be performed in MHC class II–deficient patients as early as possible, preferably before the age of 2 years. The best compatible donor available should be used. T-cell depletion of the transplant is required if the donor is not fully matched for HLA.

MHC CLASS II EXPRESSION DEFICIENCY AND CONDITIONING REGIMENS

The myeloablation conditioning protocols used in MHC class II–deficient patients have been variable.[18–20,22–24] The most frequent protocol uses a combination of busulphan and cyclophosphamide.[20] Oral busulphan is given at a total dose of either 16 mg/kg or 20 mg/kg, depending on the period-related conditioning protocol and patient age, in combination with cyclophosphamide (200 mg/kg total dose). Most patients receiving a graft from an unrelated or HLA-mismatched donor are given in vivo immunosuppression treatment (using antithymocyte globulin, campath-IG, or anti-LFA-1 with or without CD2). GvHD prophylactic treatment involves administration of cyclosporin A, from the day before transplantation and continuing until day 180, with or without methotrexate. This GvHD prophylactic treatment is given in case of no T-cell depleted graft. Use of reduced-intensity conditioning protocols should be considered at least in patients with advanced disease.[25]

IMMUNOLOGIC RECONSTITUTION AFTER HSCT

Most transplanted MHC class II–deficient patients with engraftment have normal cellular HLA class II DR expression. Low levels of HLA-DR cellular expression in several patients have been correlated with partial engraftment. MHC class II–deficient patients receiving transplants seem to display persistently low numbers of $CD4^+$ T cells. This finding is consistent with impaired thymic maturation caused by defective MHC class II expression on thymic epithelia. Despite $CD4^+$ T-cell lymphopenia, patients with complete or partial engraftment show normalization of antigen-specific T-cell stimulation and antibody production in response to immunization antigens. Of note, an impaired immune repertoire has been described for 2 patients with partial engraftment after HSCT.[23]

SUMMARY

Five conclusions can be drawn from the authors' experience in the management of patients with MHC class II deficiency.[2] First, symptomatic treatment involves the prophylactic use of antibiotics, administration of Ig, and adequate nutritional support. Second, given the invariably fatal course of typical MHC class II deficiency and the poor outcome of HSCT performed after the age of 2 to 4 years, it is highly recommended that HSCT be performed in young children, using either an HLA-identical sibling or the best available compatible donor. Third, HSCT in MHC class II–deficient patients is complicated by a high incidence of acute GvHD associated with preexisting viral infections; every effort should be made to detect viral replication and treat these infections. Fourth, $CD4^+$ T-cells remain low in number (albeit, functional) in long-term survivors

because of defective MHC class II expression by the thymic epithelial cells of the host. Finally, the lack of MHC class II expression in nonhaematopoietic cells does not seem to be detrimental for patients having undergone successful HSCT.

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