To the editor:

Is hemophagocytic lymphohistiocytosis an autoimmune disease?

Arkwright et al recently reviewed the association of autoimmunity with several inherited immunodeficiency diseases. It has been suggested that most if not all autoimmune diseases are initiated by response to a single self-antigen. Mackay and Rosen defined an autoimmune disease as a clinical syndrome caused by the activation of T and/or B cells in the absence of an ongoing infection or other discernible cause. In many cases of autoimmune diseases, autoantibodies are produced and may serve as markers of the antigen-specific B- and T-cell response.

In the context of X-linked lymphoproliferative disease (XLP) and other inherited immunodeficiency diseases, Arkwright et al. for the first time included also the immunologic disorder “hemophagocytic lymphohistiocytosis (HLH)” as an autoimmune phenomenon. HLH is characterized by uncontrolled T-lymphocyte and macrophage activation. Unrestricted release of inflammatory cytokines, such as interferon and tumor necrosis factor, is a prominent feature of primary and secondary HLH, including the Epstein-Barr virus–related form.

According to common classifications, HLH does not fulfill the criteria of an autoimmune disease (ie, an immune reaction to a more or less defined self-antigen).

We wonder, that Arkwright et al defines autoimmunity only as a bystander tissue damage due to suboptimal, chronic immune response to persisting opportunistic infection. Due to this definition, all chronic infectious disease in immune-deficient subjects would be classified as autoimmune phenomena.

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References

To the editor:

Autoimmunity in severe combined immunodeficiency (SCID)

Arkwright et al are to be complimented for their review on autoimmunity in human primary immunodeficiency diseases. While they emphasized the role of opportunistic infections, which are common in primary immunodeficiency (PID) states in the development of autoimmune disorders, we would like to draw attention to a completely different pathogenic pathway. Indeed, the apparent paradox of immunodeficiency and autoimmune coexisting in the same patient is not a real one. Recently, Candotti et al pointed out that many components of the immune system have complex functions, which often play both positive and negative roles.

In order to illustrate this point, we would like to report on 2 cases of severe combined immunodeficiency (SCID) with autoimmune diseases. SCID was not mentioned in Arkwright et al’s review as a predisposing condition to autoimmunity. Furthermore, at this young age, opportunistic infections do not seem to be related to the autoimmune phenomena. In both cases, stem cell transplantation corrected both the immunodeficiency and the autoimmune conditions.

The first patient is a 2-month-old boy whose condition was diagnosed as Omenn syndrome. Genetic analysis revealed a 1886C>T mutation in RAG1. At diagnosis he had extended erythroderma with scaling on his entire body. He also had no hair on his scalp or body as is described in Omenn syndrome. Immunophenotyping from peripheral blood showed CD3 93%, CD20 2%, CD4 28%, and CD8 68%. Proliferation studies revealed marked decreased response to various mitogens. Immunoglobulin levels were very low for IgA, IgG, and IgM, whereas the IgE level was increased to 74 IU. Skin biopsy was

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compatible with Omenn syndrome. No melanocytes were seen at that time. The patient, aged 2 months, received haploidentical peripheral stem cell transplants from his father. This was done using T-cell depletion by positive selection of CD34 cells by immunomagnetic beads. Conditioning included busulphan 16 mg/kg, cyclophosphamide 200 mg/kg, fludarabine 200 mg/m², and anti-thymocyte globulin (ATG) (fresenius) 25 mg/kg. No graft-versus-host disease prophylaxis was given after transplantation. After rejecting the graft, he received his second haploidentical transplants with T-cell depletion from his mother. Conditioning included anti-CD3 (OKT3) and thiopeta 7 mg/kg. Engraftment occurred on day +9 with complete donor chimerism. Gradually, the erythrodermia subsided and he was noted to have fair skin with white hair and white eyelashes—a picture that resembled vitiligo. No other signs of graft-versus-host disease (GVHD) were seen, and there were no gut or liver manifestations. Skin biopsy was compatible with vitiligo with melanocytes and no evidence of GVHD. Later, focal hyperpigmentation on exposed portions of his body (face, hands, and legs) started to appear with coalescence of those focal pigmentation into complete repigmentation thereafter. Also, focal pigmentation appeared on the scale, with brown hair arising from those spots later. A biopsy done from areas of pigmentation and depigmentation showed melanocytes on pigmented areas and a lack of them on the depigmented areas. Neonatal autoimmune disorder not related to maternal disease is very rare. Because vitiligo is an immunologic phenomena caused by activated T cells, we hypothesized that a T-cell-mediated autoimmune process caused the disappearance of melanocytes and vitiligo. This was corrected by stem cell transplantation, causing elimination of the autoreactive T cells that are common in Omenn syndrome. Now, 18 months after transplantation, he has brown hands and his lower legs and face are spotted with brown hair, whereas the rest of his body is only spotted by pigmentation.

The second patient was diagnosed at the age of 11 months as suffering from SCID with no T cells but with B and natural killer (NK) cells (T-B−NK+) resulting from IL-7 receptor alpha deficiency. The mutation found was a g to a base substitution causing a splice-site mutation at position –1 of intron 2 leading to complete skipping of exon 3. At diagnosis she had fever and diarrhea caused most probably by viral disease. Later, she developed severe thrombocytopenia (5000/mm³) with wet purpura. Bone marrow aspiration revealed increased number of megakaryocytes compatible with the diagnosis of idiopathic thrombocytopenia purpura (ITP) with no response to intravenous immunoglobulin (IVIG) and pulse steroids. Allogeneic bone marrow transplantation from a matched-sibling donor without conditioning or GVHD prophylaxis was performed. Two weeks after transplantation there was a gradual increase in thrombocyte numbers until full recovery. We concluded that this patient’s ITP was corrected by allogeneic bone marrow transplantation.

In summary, we reported on 2 infants with SCID and autoimmune disorders. Both conditions were corrected by stem cell transplantation. As is stated in Candotti et al’s paper, immunodeficiency and autoimmunity are not opposites. Indeed, mixed pictures could happen. Either way, stem cell transplantation is probably the correct solution for both problems.

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Response:

Redefining autoimmunity in primary immunodeficiency diseases

Schuster et al’s letter questioning our definition of autoimmunity focuses in on the fundamental impetus for our review. They are correct when they quote that autoimmune disease is conventionally defined as a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause. However, in patients with autoimmunity associated with defined primary immunodeficiency diseases (PIDs), advances in our understanding of the disease pathogenesis means that this definition has been superseded. Autoimmunity occurring in PIDs, although associated with immune self-destruction, is not usually triggered by immune intolerance to self-antigens. Autoimmune responses to self-antigens may contribute to ongoing inflammation, but the primary trigger is generally the inability of an inherently defective immune system to eradicate persisting foreign microbial antigens. The basic principles underlying the widespread tissue destruction in hemophagocytic lymphohistiocytosis (HLH) syndromes, where defined underlying defects in the immune system allows intercurrent Epstein-Barr virus (EBV) infection or other factors to trigger uncontrolled lymphocyte-initiated macrophage activation, are no different to those seen in other autoimmune conditions associated with PID. At the moment, we lack the knowledge to explain the underlying immune mechanism(s) in many autoimmune disorders, but there is no doubt that better understanding of the basis of autoimmunity in PID will provide a framework for rethinking fundamental concepts as well as treatment strategies for these conditions.

In their letter, Elhasid et al rightly point out that autoimmune phenomena may develop in some cases of severe combined immunodeficiency (SCID). As detailed in our review, autoimmune phenomena are well recognized in Omenn syndrome. Certain mutations in the RAG gene result in incomplete blockage of T-lymphocyte development. Dysfunctional T-cell clones may cause inflammation in any tissue of the body, but especially in the skin, liver, bone marrow, and brain. Other forms of SCID with aberrant T-lymphocyte development, often presenting in older children or adult as common variable immunodeficiency, may also
be associated with clinically significant autoimmunity. In contrast, in children with classical SCID in whom no T lymphocytes are present, clinical features suggestive of autoimmunity are more likely to be due to the direct consequences of infections, as the complete lack of T lymphocytes prevents the development of an autoimmune response. Elhasid et al’s second patient with T−B−NK+ SCID developed a consumptive thrombocytopenia that did not respond to steroids or high-dose intravenous immunoglobulin (IVIG) therapy, but the patient did finally respond to matched-sibling bone marrow transplantation. Considering the temporal relationship to the other symptoms of viral infection, it is likely that rather than the thrombocytopenia being ITP, it was directly caused by the virus infection. As emphasized in our review, immunomodulation and treatment of infection is often a better treatment strategy than immunosuppression alone in children with primary immunodeficiency and suspected autoimmune phenomena, as immunosuppression may exacerbate the underlying infectious disease and result in increased morbidity and mortality.

Finally, as stated in our review and reiterated by Elhasid et al, in children with an underlying PID, autoimmunity and the inability to effectively eradicate infection should both be viewed as features of dysregulated immunity. Correcting the underlying immunodeficiency by stem cell transplantation often corrects both clinical problems. Although stem cell transplantation had in the past been considered, but not often used, as a possible treatment option for autoimmunity where no underlying primary immunodeficiency can be found, advances in the safety and effectiveness of this therapy have recently lead to a revival in interest in this treatment modality.

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To the editor:

Long-term follow-up on a patient with incomplete POEMS syndrome undergoing high-dose therapy and autologous blood stem cell transplantation

Jaccard et al recently reported a series of 5 patients with polynuropathy, organomegaly, endocrinopathy, monoclonal gammapathy, and skin changes (POEMS) syndrome who underwent high-dose chemotherapy followed by autologous stem cell transplantation. In 2001, first reports of single patients after autologous transplantations were published. So far, all published cases show dramatic improvement in clinical manifestations, especially of polyneuropathy, and no relapses have been reported after autologous stem cell transplantation. However, data on long-term follow-up are extremely rare. Median follow-up of patients published by Jaccard et al was 36 months, with the first patient being assessed 58 months after transplantation.

Here, we report a patient who developed multifocal osteosclerotic myeloma in 1994 at the age of 30. Osteosclerosis was diagnosed in the skull, both femur, and the pelvis, and the diagnosis was confirmed by biopsy. Bone marrow histology revealed no increase in the number of plasma cells. Due to progressive polyneuropathy predominating the lower limbs, the patient rapidly became paraplegic. Muscular strength of the arms progressively polyneuropathy predominating the lower limbs, the patient rapidly became paraplegic. Muscular strength of the arms and legs was considerably reduced as well. All muscular stretch reflexes were absent. There was hypesthesia and paresthesia of the lower extremities. Electroneurographic studies revealed that nerves of the lower extremities had no motorial or sensoric nerve action potentials, and F waves were absent. Also, nerves of the upper extremities showed electroneurographic abnormalities with reduction of nerve conduction velocity and nerve amplitudes. Incomplete polyneuropathy, hepatomegaly and lymphadenopathy, peripheral edema, thrombocytosis (700 000/µL), and pleural effusion was diagnosed according to Gheradi et al. In contrast to other published cases, no monoclonal immunoglobulin was detected (immunofixation electrophoresis of serum and urine, on follow-up free light chains by nephelometry).

Although therapy was started (melphalan, prednisolone), neurological symptoms progressed further. After ineffective tamoxifen medication, the patient received 4 cycles of ifosfamide (2 × 3000 mg/m²). Peripheral blood stem cells were collected and the patient underwent high-dose chemotherapy with total body irradiation (12 Gy) and melphalan (140 mg/m²) in April 1996. The posttransplantation course was uneventful except for neutropenic fever and severe mucositis. Six years after transplantation the patient is still in good clinical condition. His neurologic status improved considerably; the patient is able to get up and walk short distances on crutches including going upstairs a few steps. Extensor and flexor muscles of the feet were still plegic. All other muscles of the upper and lower extremities had nearly normal strength. Hypesthesia and pallesthesia of the lower extremities had slightly improved. All muscular stretch reflexes were absent. Electroneurographic parameters of nerves of the upper extremities normalized. Some of the sclerotic lesions improved (femura, pelvis), some remained unchanged (skull), and no new osteosclerotic lesions occurred. Thrombocyte counts returned to normal, and peripheral edema disappeared. Observed clinical and laboratory improvements could
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