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LETTER TO THE EDITOR

Severe chronic psychosis after allogeneic SCT from a schizophrenic sibling

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Schizophrenia is a life-long disorder, usually starting at early adulthood and consisting of remitting or chronic psychosis and functional decline.

There is ample evidence that immune processes play a role in schizophrenia.[1–4] More than 20 different auto-antibodies are at elevated levels in patients with schizophrenia as compared to controls.[5] Autoimmune diseases (AID), such as thyrotoxicosis, celiac disease, acquired hemolytic anaemia, interstitial cystitis and Sjögren's syndrome, but also atopic diseases, have higher prevalence rates among patients with schizophrenia.[6,7] The strongest genetic association with schizophrenia is found in the MHC genes, including loci that influence immune responses.[8] Further evidence for an autoimmune component comes from the lower incidence of schizophrenia in men who used glucocorticosteroids for somatic diseases (odds ratio 0.52).[9] It is unclear if immune processes play a key role in all patients with schizophrenia, or only in ~30–40% of them.[10,11]

A common characteristic of AID[12] and severe allergies[13] is their favourable response to immune ablation and rescue with SCT. Accordingly, we (IES and DWvB) searched for transplant cases suffering from coincident schizophrenia.[14,15] No such cases had been discovered, but one of us (GT) retrieved the history of a patient who developed severe psychosis after receiving a BM transplant from his schizophrenic brother.

The patient (born 1940) had a blank psychiatric history. He was retired, married and had two adult children. At the age of 67 he developed fatigue and skin ecchymoses, and he was diagnosed with chronic lymphocytic leukemia (CLL) and bone marrow aplasia, requiring weekly blood transfusions. Chemotherapy (two courses of CY), and treatment with cyclosporin A, rituximab and prednisolone did not improve his CLL/aplastic anemia. In 2007 he received an allogeneic peripheral blood SCT from one of his brothers, who was the only HLA-matched family member. This brother (born 1952) had schizophrenia since early adulthood and he required treatment with multiple antipsychotic agents. No other first-degree relatives suffered from schizophrenia. The donor also had a history of Lyme disease 8 years before. Serology showed positive IgG and negative IgM for Lyme disease, and PCR was negative for *Borrelia burgdorferi* DNA, consistent with inactive prior infection. The donor used doxycycline 100 mg twice daily, starting 4 days before the stem cell collection, as a safety measure to prevent transmission. The patient was conditioned with fludarabine and CY, followed by an infusion of 5.0×10^6 $CD34^+$ cells/kg from the peripheral blood of his brother. Tacrolimus was administered to prevent GVHD. He never received steroids, and did not develop graft-vs-host reactions. He had complete hematologic recovery and reached full hematopoietic chimerism (>97% donor cells 4 weeks after SCT). We tapered off tacrolimus 4 months after the SCT, because of decreasing blood counts. A few weeks later, when off tacrolimus, he developed acute psychotic symptoms: frequent hallucinations (running commentary and threatening voices), bizarre and non-bizarre delusions, and thought broadcasting with clear consciousness. Insight and judgment were poor. He described his mood as 'angry', with a flat affect. When he developed suicidal and homicidal ideation, he was admitted to a psychiatric clinic. Neurological evaluation, magnetic resonance imaging and electroencephalography revealed no abnormalities. Extensive medical work-up did not reveal metabolic disorders, underlying infections and neoplasms. Results of lumbar puncture were normal, and screenings for viruses (including Herpes Simplex Virus and Human Herper Virus-6), bacteria, fungi and Lyme disease were all unremarkable. He was treated with risperidone 3 mg and citalopram 20 mg, unsuccessfully. Under the working diagnosis of delirium, all medications were discontinued and haloperidol 1 mg was administered, which was not helpful either.

The patient's family decided for comfort care only and the patient was lost to follow-up. He died in 2010, of unknown cause.

The following differential diagnoses were considered and dismissed:

Delirium: Acute onset of psychotic symptoms in a 68-year-old man after somatic disease. However, the 4-month interval between transplantation and onset of psychosis is atypical. Furthermore, discontinuation of all medication did not improve his condition, nor could any somatic disorder be identified.

Endogenous schizophrenia: The patient was genetically predisposed to schizophrenia, given his brother had this disease. However, acute onset at the age of 68 is rare,[16] especially in males.[17] Age of onset is strongly correlated among affected siblings, and differences in onset of more than 10 years are very rare.[18]

Tick-borne infection transmitted through stem cells: The stem cell donor had Lyme disease 8 years earlier. Transfer of tick-borne pathogens might have caused psychotic symptoms. However, the donor was *Borrelia* IgM and PCR negative and received doxycycline before stem cell extraction.

Therefore, adoptive transfer of schizophrenia is the most appealing etiology, not only by exclusion, but also in view of the increasing evidence that some forms of schizophrenia have an autoimmune origin. Although the transplanted patient fulfills these criteria, a formal diagnosis was never made given his very unusual age of onset and potential relation to the SCT.

Adoptive transfer of AIDs seems to be rare, as we are aware of only 21 cases reported so far among ~200 000 long-term survivors of allogeneic SCTs. Stem cell donors are routinely subjected to complete medical examination; therefore chances are small that AID is overlooked. The 21 cases include thyroiditis (10 cases),[19] vitiligo (3),[20–22] psoriasis (2),[23,24] type I diabetes mellitus (2),[25] celiac disease (1),[26] thrombocytopenia (1),[27] polyglandular syndrome type II (1)[22] and systemic lupus erythematosus (1).[28] Moreover, not only AIDs may be transferred by SCT but also other immune diseases, such as allergies.[13] Adoptive transfer of AIDs and allergies is thought to be mediated by transfer of donor lymphocytes. This suggests that the subform of schizophrenia in the patient was mediated by lymphocytes.

Based on this single case report, we obviously cannot prove an immune pathogenesis of schizophrenia. However, the report supports the hypothesis of immunological involvement in schizophrenia pathogenesis and we suggest that physicians and patients involved in SCT take into consideration the possibility that schizophrenia may be transmitted by the transplant.

Taking it one step further, coexisting schizophrenia might not *per se* be considered as a contraindication in patients with standard transplant indications, but rather as an opportunity for inducing remission of the psychotic process and as a potential area of research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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