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Erosive Rheumatoid Arthritis After Bilateral Hand Transplantation

Brittany L. Adler, MD,

Department of Rheumatology, Johns Hopkins University School of Medicine; Baltimore, MD, USA

Jemima Albayda, MD,

Department of Rheumatology, Johns Hopkins University School of Medicine; Baltimore, MD, USA

Jamie T. Shores, MD,

Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine; Baltimore, MD, USA

W.P. Andrew Lee, MD,

Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine; Baltimore, MD, USA

Gerald Brandacher, MD, and

Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine; Baltimore, MD, USA

Clifton O. Bingham III, MD

Department of Rheumatology, Johns Hopkins University School of Medicine; Baltimore, MD, USA

Background:

Rheumatoid arthritis is a systemic autoimmune disease that primarily affects joints. The pathogenesis is unknown but likely involves environmental and genetic factors.

Objective:

To describe a patient whose rheumatoid arthritis seems to be a combination of environmental and genetic factors.

Case Report:

A previously healthy 26 year-old woman of Filipino descent developed digital gangrene from meningococcemia, resulting in bilateral mid-forearm and below-knee amputations. At age 33, the patient received allogeneic bilateral hand and forearm transplants. Neither the donor nor the recipient had a personal or family history of rheumatoid arthritis. The immunotherapy regimen consisted of a bone marrow cell infusion from the donor and

maintenance tacrolimus monotherapy. The early postoperative course was uneventful except for a skin rash (biopsy-confirmed Banff grade I rejection) that resolved with bolus steroids.

The patient developed subacute bilateral hand pain and swelling one year after transplantation, but the graft otherwise continued to function normally. The patient's elbows, shoulders, and knees were not affected. Results of blood tests for rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and antinuclear antigen were negative, but the C-reactive protein level was elevated to 6.5 mg/dL (619.01 nmol/L) (normal <0.31 mg/dL [<29.52 nmol/L]).

Physical examination was notable for palpable bilateral synovitis in the metacarpophalangeal, proximal interphalangeal, and wrist joints confirmed on ultrasonography and magnetic resonance imaging, which showed synovitis and effusions, moderate tenosynovitis, and erosive changes (Figure a-d). We added methotrexate and prednisone therapy to the maintenance tacrolimus therapy. The patient initially responded but 3 years later developed new swan-neck deformities with radiographic erosions (Figure e-f) despite ongoing immunosuppression.

Discussion:

According to the 2010 rheumatoid arthritis classification criteria recommended by the American College of Rheumatology and the European League Against Rheumatism (1), this patient has rheumatoid arthritis based on her small-joint involvement, elevated levels of inflammatory markers, chronicity of symptoms, and erosions. She did not have detectable rheumatoid factor or anti-cyclic citrullinated peptide antibodies, but 20% to 40% of patients with rheumatoid arthritis are seronegative.

Rheumatoid arthritis is mediated through genetic susceptibilities, environmental triggers, and dysregulated immunologic and inflammatory pathways. The greatest genetic risk is the expression of specific HLA alleles, which encode proteins involved in antigen presentation (2). This patient's HLA alleles (*A24, 34; C4; B75; Bw6; DRB1*15:02, DRB5*51; DQA1*01, DQB1*06:01/06:105; and DPB1*01:01, 04:01*) included the *HLA-DQB1*06* epitope and the *DQB1*06-DRB1*15* haplotype, both of which are more common in some populations with rheumatoid arthritis (3, 4). The donor's HLA alleles (*A1, 2; B8, 44; Cw4, 7; DR7, 17; DQ2; and DR52, 53*) did not include any high-risk alleles. These conditions suggest that the recipient but not the donor was genetically predisposed to rheumatoid arthritis. We believe that this patient may have reacted against novel antigens in the transplanted hands and forearms, which would explain the temporal association between the transplantations and the onset of rheumatoid arthritis. It also would explain the involvement of donor joints but not native ones; it is not possible to determine whether her feet might also have been involved because the patient has prosthetic legs. Erosive arthritis developed despite ongoing immunosuppression with tacrolimus, which shows how complex the pathogenesis of rheumatoid arthritis is.

To our knowledge, this is the first report of rheumatoid arthritis in a hand transplant recipient. Whether it constitutes an atypical transplant rejection is unclear. Only

approximately 130 hand transplantations have been done since the first one in 1998 (5), and we are just beginning to understand the long-term outcomes for these patients.

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Figure.
Swan-neck deformities of the fourth and fifth fingers.