

## Letter to the Editor

**Bone marrow transplantation for monoallelic signal transducer and activator of transcription 1 deficiency**

To the Editor:

Signal transducer and activator of transcription (STAT) 1 plays an important role in the response of immune and nonimmune cells to stimulations. Complete absence of STAT1 results in susceptibility to mycobacteria, viral, and fungal infections. Monoallelic mutations in STAT1 were identified among patients with diverse immune abnormalities such as chronic mucocutaneous candidiasis, autoimmunity, bowel inflammation, and brain aneurysms.<sup>1</sup> In these patients, STAT1 phosphorylation was increased; hence, the designation gain-of-function mutation. The cause for the variability in immune phenotype might be related to the specific STAT1-mutated regions disrupted. Mutations in the DNA-binding domain (DBD) are frequently de novo mutations and associated with fatal infections at an early age. In contrast, STAT1 coiled-coil mutations are commonly recognized in multiple family members in association with various degrees of candidiasis with or without strokes.<sup>2,3</sup> Patients with the T385M mutation in the DBD were reported to experience progressive decline in immunity, culminating in combined immunodeficiency and death at an early age.<sup>3-6</sup>

Management of patients with chronic mucocutaneous candidiasis and STAT1 mutations has been primarily supportive, with antimicrobial prophylaxis and immunoglobulin replacement, immune suppression, and modulation for autoimmune manifestations. However, these treatments do not correct the immune deficiency. There are reports of only 3 patients with STAT1 defects who received allogeneic hematopoietic stem cells transplantation (HSCT), but none survived.<sup>7,8</sup> Here, we report the first successful HSCT in a patient with DBD STAT1 mutation. This patient's extensive mutation analysis as well as immune evaluations have been previously reported.<sup>4</sup>

The male patient suffered from age 1.5 years multiple episodes of oral thrush and ulcers, as well as lip and facial hyperkeratotic lesions with *Candida albicans* growth. *Candida* was also cultured from groin lesions. Examination of the nails revealed paronychia. He also suffered from pneumonia and otitis media. There was no evidence for intestinal or endocrine abnormalities, although the patient exhibited short stature. During follow-up, there was progressive decline in the number of CD4 and B cells. T cells demonstrated persistently reduced proliferative responses to mitogens and antigens, reduced secretion of IL-2 and INF- $\gamma$ ,<sup>4</sup> and impaired production of antibodies in response to some vaccines (see Table E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Sequencing of the STAT1 gene identified a de novo mutation resulting in a putative T385M change. STAT1 protein expression and phosphorylation were found to be reduced in the patients' T cells, but increased in EBV-transformed lymphoblasts.<sup>4</sup>

At age 7 years, the patient received unmanipulated bone marrow HSCT from his HLA-identical brother who had normal STAT1 gene sequencing and normal immune function. Magnetic

resonance imaging of the brain with contrast material and cardiac echo before HSCT did not reveal any abnormality. The patient received myeloablative conditioning with busulfan 16 mg/kg and cyclophosphamide 200 mg/kg. Graft versus host disease (GvHD) prophylaxis consisted of cyclosporine A (target levels, 175-200  $\mu$ g/L) and methylprednisolone (2 mg/kg), as previously described.<sup>9</sup> Acute GvHD involving the skin and the gastrointestinal tract, confirmed by biopsy, developed at 7 and 17 days, respectively, after HSCT, which improved with pulse-dose methylprednisolone,<sup>10</sup> oral budesonide, sirolimus, and mycophenolate mofetil. Massive lower gastrointestinal bleeding began 1 month after HSCT, which was resistant to medical management. Technetium 99m-labeled red blood cell studies suggested an active lower gastrointestinal bleed possibly at the right lower quadrant. Computerized tomography angiogram showed contrast material extravasation in the terminal ileum with engorged adjacent mesenteric vessels indicative of localized bleeding (Fig 1, A) with no evidence for small vessel vasculopathy. Bowel wall thickening in the terminal ileum and colon was also noted, suggestive of GvHD. Image-guided embolization failed; therefore, the distal ileum was resected and an end-ileostomy was created, leading to resolution of the bleeding. The resected area contained 2 hemorrhagic linear ulcers as well as focal "moth-eaten" regions (Fig 1, B). Microscopically, the moth-eaten regions corresponded to foci of markedly increased crypt apoptotic bodies (Fig 1, C). Also seen were aseptic thrombi within small veins and arteries adjacent to the ulcerated areas (Fig 1, D), as well as thick-walled arteries near the mucosal surface (Fig 1, E). There was no evidence of an active vasculitis and special stains for fungi, and immune-histochemical staining for adenovirus and CMV was negative. The patient suffered from hemorrhagic cystitis, pulmonary aspergillosis, and other complications, which resolved. Currently, 1.5 years after HSCT, the patient is clinically well, attending school, and gaining weight. The oral ulcers have not reoccurred, and there is no evidence for active fungal or other opportunistic infections. Immunosuppression has been recently discontinued with no exacerbation of GvHD. Laboratory evaluations consistently demonstrate more than 95% donor chimerism. Recent lineage-specific assessment indicates more than 95% donor T and B cells, monocytes, and neutrophils.

The decision to have the patient undergo a transplant, similar to other primary immune deficiencies that are not immediately life threatening, needs to take into consideration many factors. These factors include the expected "natural course" of the disease, the patients' current morbidity, and donor availability, which contribute to the risks and benefits assessment of the transplant for a specific patient. In other patients, STAT1 T385M mutation has been associated with combined immunodeficiency, recurrent and fatal infections, endocrine and hematological autoimmunity, and severe colitis.<sup>3-5,11</sup> Indeed, the patient described here has also demonstrated T-cell dysfunction and a gradual decline in B-cell numbers. The patient suffered recurrent infections as well as stunted growth, yet he had not yet developed severe organ damage nor was he affected by infections such as EBV or CMV that would complicate conditioning and transplantation outcome. Moreover, the patient had an optimal HLA-identical donor, which is associated with reduced frequency and severity of GvHD and

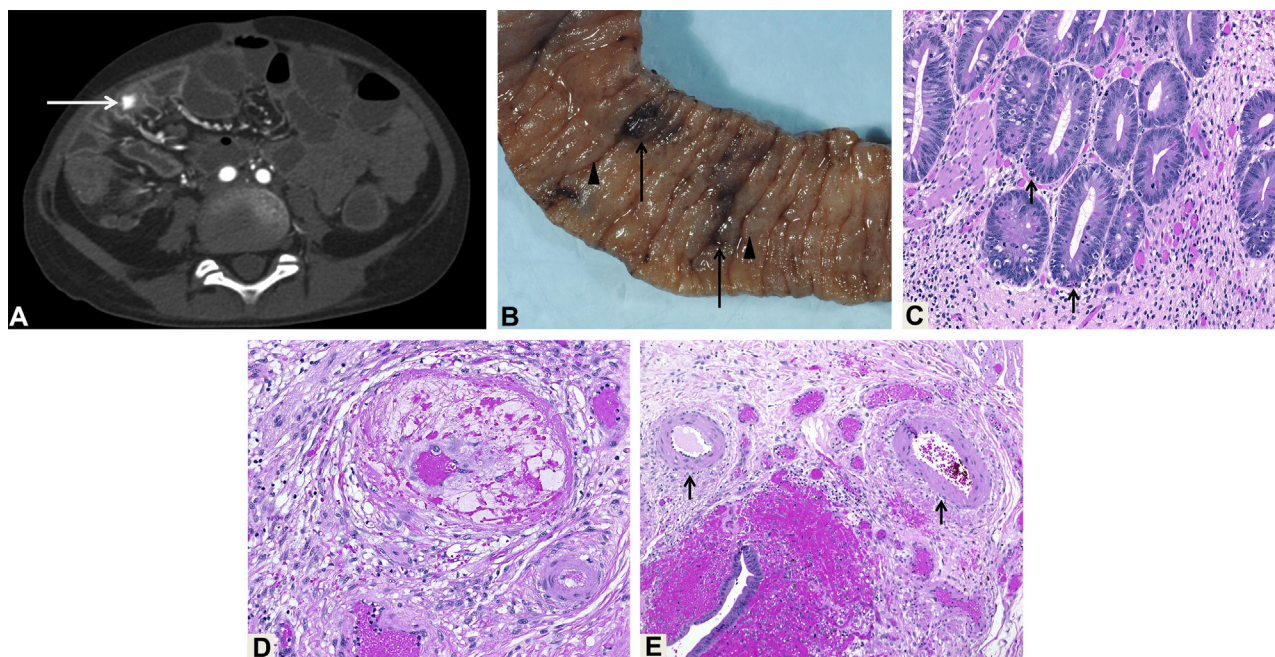


**FIG 1.** Imaging and histology of patient's gastrointestinal track following massive bleed. **A**, Computed tomography angiogram study, demonstrating intraluminal contrast extravasation in terminal ileum (white arrow) suggestive of active bleeding. **B**, Resected ileum showing linear hemorrhagic ulcers (arrows) together with an adjacent "moth-eaten" appearance (arrowheads). **C**, Photomicrograph demonstrating marked increase in basal crypt apoptosis (arrows). Hematoxylin and eosin, original magnification  $\times 200$ . **D**, Photomicrograph of an organizing, aseptic subacute thrombus within a submucosal venule. Hematoxylin and eosin, original magnification  $\times 200$ . **E**, Photomicrograph of thickened submucosal arteries very close to the mucosal surface (bottom left). Hematoxylin and eosin, original magnification  $\times 100$ .

improved HSCT outcome. All these factors contributed to the decision to proceed with HSCT.

Interestingly, despite using an HLA-identical donor, the patient developed severe acute GvHD. Whether the immune abnormalities associated with STAT1 mutations predispose to more severe GvHD is not clear. Yet, some patients suffer from immune dysregulation even after HLA-matched sibling HSCT transplantation.<sup>8,12</sup> The patient described here also suffered from severe bleeding following HSCT, possibly related to localized vascular changes. Arterial vasculopathy has been reported infrequently among pediatric patients following allogeneic HSCT, yet the occurrence of gastrointestinal and brain bleeding in 3 of the 4 patients with transplanted STAT1<sup>7,8</sup> is worrisome. Whether the bleeding is related to the increased frequency of vasculitis already noticed among patients with STAT1 defects,<sup>6</sup> or to increased susceptibility of patients' tissues and vessels to bleeding following chemotherapy, demands further study. Regardless of the cause, reporting the challenging posttransplant course should help other patients, families, and health care providers in the decision and preparation for the management of STAT1 deficiency. Importantly, the myeloablative-conditioning regimen that we used likely contributed to the establishment of full donor chimerism, suggesting that such approach could be beneficial for patients with DBD STAT1 mutations.

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**TABLE E1.** Immune function of the patient with STAT1 at different ages

| Immune parameters          | Age          |              |              |              |                     |
|----------------------------|--------------|--------------|--------------|--------------|---------------------|
|                            | 2.7 y        | 4 y          | 5 y          | 6.3 y        | Normal range at 6 y |
| CD4+ T cells/ $\mu$ L      | 788          | 617          | 756          | 504          | 300-2000            |
| CD8+ T cells/ $\mu$ L      | 391          | 420          | 538          | 398          | 300-1800            |
| PHA stimulation*           | 39.8%        | 37.7%        | 39.6%        |              | >50.0%              |
| CD19/20+ B cells/ $\mu$ L  | 644          | 256          | 381          | 207          | 200-1600            |
| IgG (g/L)                  | 6.0          | 6.0          | 6.9          | 5.5          | 5.0-14.6            |
| IgA (g/L)                  | 0.4          | 0.5          | 0.8          | 0.7          | 0.3-2.0             |
| IgM (g/L)                  | 0.3          | 0.2          | 0.2          | <0.3         | 0.2-2.5             |
| Tetanus antibodies (IU/mL) | >0.1         | 0.09         | 0.14         | 0.33         | $\geq$ 0.1          |
| Measles antibodies         | Equivocal    | Undetectable | Undetectable | Undetectable | Detectable          |
| Mumps antibodies           | Undetectable | Undetectable | Undetectable | Undetectable | Detectable          |
| Rubella antibodies         | Detectable   | Detectable   | Detectable   | Detectable   | Detectable          |
| Varicella antibodies       | Undetectable | Undetectable | Undetectable | Undetectable | Detectable          |

\*Thymidine incorporation into peripheral mononuclear cells 4 d after stimulation with PHA.