

Delay of the diagnosis of Graft *versus* host disease in an autologous stem cell transplant recipient: a case report and literature review

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ABSTRACT

Background: Autologous stem cell transplantation is an alternative to allogeneic stem cell transplantation to minimize the complications of genetic discrepancies in mismatching donor cells to the recipient. One such complication, graft-versus-host-disease (GVHD), should theoretically not occur with autologous transplantation given the identical similarity in cells. The literature supporting GVHD in these patients is reviewed and a case presentation of insidious GVHD is demonstrated to emphasize awareness of this elusive disease. A timely and accurate diagnosis can minimize unnecessary hospitalizations, repetitive infectious disease evaluations and maximize utmost patient care in autologous stem cell transplantation patients.

Objective: This case highlights the prevalence of graft-versus-host disease occurring in this unique patient population and serves to help elucidate the mechanisms behind this autogenic phenomenon.

Case Description: The patient is a sixty-six-year-old man with a history of multiple myeloma and recent autologous stem cell transplantation who developed a non-specific cutaneous eruption in the setting of refractory diarrhea. The patient was admitted for further work-up and hypothesized to have autologous GVHD readily responsive to steroid therapy.

Conclusions: This case report and literature review highlights the necessary cognizance and recognition of the phenomenon of autologous GVHD. The presentation occurs early after ASCT with non-specific gastrointestinal and cutaneous findings. Misdiagnosis can result in a lack of appropriate treatment and unneces-

sary hospitalizations. GVHD presenting in autologous stem cell transplantation patients is an elusive diagnosis which should be swiftly recognized and treated.

INTRODUCTION

A sixty-six-year-old man with a history of multiple myeloma and recent autologous stem-cell transplant 4 months prior presented with the chief complaint of a generalized drug eruption. The patient had recently received a cycle of pomalidomide therapy one week prior to developing an exanthematous dermatitis on his trunk and proximal extremities. Upon further history, the patient had received pomalidomide cyclic therapy several times without a similar associated reaction. The patient had also been treated with lenalidomide, bortezomib and dexamethasone after the diagnosis of multiple myeloma one year prior. The patient was then switched to cyclic pomalidomide, cytoxan, and dexamethasone; high dose melphalan was given prior to the autologous stem cell transplantation (ASCT).

After the ASCT, the patient's course was complicated by aspergillosis pneumonia and numerous episodes of refractory, secretory diarrhea. Furthermore, the diarrhea was persistent and resulted in three subsequent hospitalizations, as well as the current hospitalization, given the presentation of secondary dehydration and hypovolemic shock. An infectious etiology was not identified in any of the previous admissions.

The patient's past medical history included chronic obstructive pulmonary disease and carotid stenosis. His hospital medications included lovenox, acyclovir, tiotropium, fluticasone, imodium and protonix; no new medications were initiated and poma-



Fig. 1. Multiple pink to red coalescing papules over the proximal thighs.

lidomide was held. Skin examination revealed numerous and diffuse pink to red coalescing papules over the bilateral upper extremities, lower abdomen, and proximal thighs in a cachectic light-complected adult male (Figure 1). Nail findings included ten-nail involvement with longitudinal ridging, thinning and onycholysis (Figure 2). Inspection of the oral mucosa revealed central atrophy of the dorsum of the tongue (Figure 3).

Laboratory findings revealed leukopenia with a white blood cell count of $2.2 \times 10^3/\mu\text{L}$, anemia with a hemoglobin of 10 g/dL, and thrombocytopenia with platelets of $63 \times 10^3/\mu\text{L}$. Stool examination revealed cultures with no growth, negative ova and parasites, and negative *Clostridium difficile*, *Shiga* toxin, *Cryptosporidium* antigen, *Giardia* antigen,

Vibrio, *Yersinia*, *Microsporidia*, *Aspergillus* galactomannan and adenovirus studies.

Upon consultation, a 4 mm punch biopsy from the right thigh was performed. Topical hydrocortisone cream 2.5% was applied twice daily. The patient was followed for several days as his stool studies returned negative, yet his secretory diarrhea and non-specific skin eruption persisted. The hypothesis of graft-versus-host disease (GVHD) was then formulated as the patient simultaneously underwent a colonic biopsy to further characterize his refractory diarrhea. The colonic biopsy revealed apoptotic bodies within the crypts, suggestive of a grade 1 GVHD reaction.

Discussion amongst the consultants then ensued given his history of an autologous SCT; was this



Fig. 2. Nail findings included ten-nail involvement with longitudinal ridging, thinning and onycholysis.

Fig. 3. Central atrophy of the dorsum of the tongue with leukoplakia.



reaction possible in his clinical context? The skin biopsy had revealed a lymphocytic infiltrate with an interface dermatitis and apoptotic keratinocytes consistent with acute cutaneous GVHD (Figure 4). The decision was then made to begin intravenous steroid therapy given colonic and skin biopsies as

well as suggestive clinical history and negative infectious gastrointestinal culprits. The patient's diarrhea improved and his dermatitis resolved rapidly (Figure 5). Given the concern for opportunistic infections, intravenous steroid therapy was only given for one day; a two-week oral prednisone taper

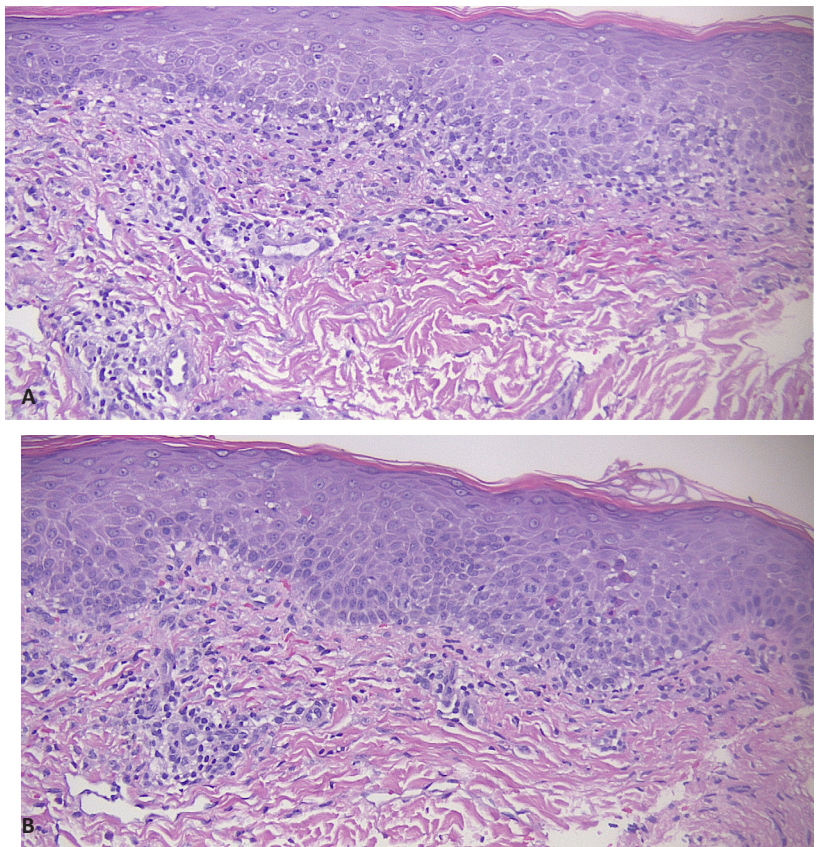


Fig. 4. *A*, Punch biopsy revealed a lymphocytic infiltrate with an interface dermatitis and necrotic keratinocytes. Eosinophils were not identified. *B*, Higher magnification.



Fig. 5. Resolution of red plaques on extremities after intravenous steroid therapy.

then ensued, followed by 10 mg oral prednisone for daily maintenance without further complications and complete resolution of symptoms.

DISCUSSION

Graft versus host disease (GVHD) is an immunologic phenomenon involving the attack of the recipient's skin, gastrointestinal tract and liver by donor lymphocytes. The main predictor of development is the mismatch of histocompatibility antigens. Patients undergoing ASCT do not have the dissimilarity in donor cells, creating an enigma for similar presenting symptoms of GVHD in this distinctive patient population. Identical autoimmune mechanisms crafting the characteristic symptomology of diarrhea, non-specific skin rashes and transaminitis, do not seem plausible, yet one cannot deny the congruous presentation.

Patients less than sixty-five years old with multiple myeloma are eligible for autologous stem cell transplantation (ASCT); three-drug combinations are employed for induction, and involve a novel proteasome inhibitor, bortezomib, commonly in adjunctive therapy with dexamethasone and thalidomide¹. After three to six induction cycles, high dose melphalan is utilized prior to ASCT¹. The phenomenon of acute GVHD-like disease in patients undergoing ASCT has been recently identified and contemplated over the past several years. An estimated prevalence of development has been cited and ranges from 2-13%¹⁻⁴. Additionally, the prevalence has been found to be consistently higher among patients with multiple myeloma. A case series of 388 autologous stem cell transplants patients followed over a 6

year period noted an overall prevalence of 4% with the prevalence in multiple myeloma patients higher at 6%, compared to 3% associated with Non-Hodgkin's lymphoma⁵. Additionally, patients with tandem or second stem cell transplantations are at even higher risk for disease, presumably due to repetitive exposure to potent chemotherapeutic agents, one of several plausible inciting factors^{3,6}.

The majority of cases have been described as having a relatively benign course with a mild skin rash and gastrointestinal involvement^{2,4}. In a review of 681 ASCT patients, where the diagnosis of GVHD was defined by mucosal abnormalities, persistent symptoms, and histologic changes of apoptotic cryptic cells, the proportion of gastrointestinal involvement due to GVHD was found to be approximately 13%⁴. The vast majority of these patients presented with nausea and vomiting and less than half with diarrhea⁷. The mild GI cases of GVHD respond relatively well to steroid therapy^{4,7}. Cutaneous manifestations are ubiquitously present; however, the associated dermatitis is very non-specific and may manifest as waxing and waning pink to red papules on the trunk and extremities. In a case series of ASCT, 7/96 developed GVHD and all had cutaneous findings with characteristic skin biopsy findings⁸. Table 1 highlights the case reports of autologous GVHD; all reports demonstrated a non-characteristic dermatitis, commonly in addition to fever and nausea. The medications received are displayed and were analogous, which underlies the theories behind conceivable pathogenic mechanisms due to pharmacology.

Table 1. Review of case reports of multiple myeloma patients developing GVHD s/p auto-SCT presenting with cutaneous and gastrointestinal manifestations.

| Patient | Therapies received | Days after ASCT | Presenting symptoms | Time to diagnosis | Clinical outcome |
|----------------------|---|-----------------|---|-------------------|---|
| 55 yo W ² | Bortezomib, dexamethasone, cyclophosphamide, G-CSF, melphalan | Day 24 | Fever, nausea, anorexia, diffuse red papular rash | 21 days | Fatal; refractory to steroid and tacrolimus |
| 67 yo M ¹ | Bortezomib, dexamethasone, thalidomide, melphalan | Day 84 | Nonspecific rash, diarrhea and severe respiratory failure | 7+ days | Received antibiotics, then steroids; suffered from bronchiolitis obliterans syndrome |
| 59 yo M ⁶ | Bortezomib, prednisone, melphalan | Day 19 | Fever, diffuse, erythematous and maculopapular rash | 11+ days | Persistent skin rash (day 150) requiring a repeat prednisone taper; complicated by PCP pneumonia |
| 49 yo M ³ | Cyclophosphamide, melphalan, G-CSF; second ASCT | Day 23 | Generalized erythematous rash, diarrhea | 1-17 days | Prednisone course, etanercept, daclizumab, alemtuzumab; expired |
| 49 yo M ³ | Dexamethasone, cyclophosphamide, G-CSF, melphalan, second ASCT | Day 14-21 | Generalized rash, diarrhea | 14-21 days | Prednisone, etanercept, ocreotide, TPN, expired |
| 50 yo M ³ | Dexamethasone, bortezomib, thalidomide, melphalan, cyclophosphamide, G-CSF | Day 17-41 | Diarrhea, erythematous rash | 17-41 days | Prednisone, budesonide, alemtuzumab, expired |
| 61 yo F ⁷ | Specified as 3 courses of chemotherapy, lenalidomide prior to necessary second ASCT | Day 7 | Fever, vomiting, diarrhea, rash on trunk and extremities | 41+ days | Treated with cyclosporine, mycophenolate mofetil, infliximab; course complicated with a fall resulting in a subdural hematoma and sepsis; patient expired |

Several hypotheses have been postulated over the explanation of GVHD after ASCT. Given the skewed proportion of patients with multiple myeloma, the secondary effects of the induction chemotherapeutic agents utilized must be considered. One hypothesis focuses on the use of high dose melphalan prior to transplantation, which may tamper lymphocytes and their respective regulatory functions². The proteasome inhibitors are also under scrutiny, particularly bortezomib, which induces apoptosis, and residual cells may present as self-antigens to cytotoxic T lymphocytes^{1,2,9}. Another speculated effect of proteasome inhibitors is the increased lineage of Th17 cells, which are responsible for inflammatory autoimmune diseases⁹.

Lastly, others speculate that this phenomenon may be a separate entity altogether than the traditional realm of GVHD as autologous GVHD has not been shown to present in both acute and chronic forms¹⁰.

The rarity of this diagnosis also leads to management difficulties due to the delay in diagnosis. Recurrent diarrhea, as exemplified in this case report, may lead to repeated infectious disease evaluation given the associated risk of opportunistic infections in this immunosuppressed patient population. A case series of 8 patients with autologous GVHD, as demonstrated by cutaneous and gastrointestinal biopsies demonstrated a mean duration between transplant and diagnosis of 29 days⁹. Thus, the symptoms present relatively early after ASCT when other differential diagnoses

may confound the clinical picture. As summarized in Table 1, the definitive diagnosis was not made until a range of 7-41 days after initial presentation in the reviewed 7 patients.

CONCLUSIONS

In summary, this case report highlights the necessary cognizance and recognition of the phenomenon of autologous GVHD. The presentation occurs early after ASCT and presents with non-specific gastrointestinal and cutaneous findings which may mimic more common viral and bacterial etiologies. Misdiagnosis can result in a lack of appropriate treatment and unnecessary hospitalizations. The patient presented had numerous admissions for secretory diarrhea and a 4-month delay in the clinical diagnosis despite persistent negative testing for an infectious etiology. Steroid therapy resulted in swift resolution of symptoms. GVHD presenting in autologous stem cell transplantation patients is an elusive diagnosis which should be timely recognized and treated.

CONFLICT OF INTEREST

All authors deny any potential conflicts of interest, sources of funding and/or other relationships requiring disclosure.

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