

Graft-versus-host disease

Contrast media triggering cutaneous graft-versus-host disease

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Summary:

Adverse reactions to iodinated contrast media are varied and known to develop in patients with asthma and a history of allergy. We describe three successful allogeneic bone marrow transplantation (BMT) patients, who all developed dermal graft-versus-host disease (GVHD) after receiving contrast media. Cutaneous GVHD triggered by contrast media has not been reported to date and has implications for the assessment, monitoring and treatment of patients during the post-transplant period.

Bone Marrow Transplantation (2002) 29, 899–901. DOI: 10.1038/sj/bmt/1703564

Keywords: bone marrow transplantation; graft-versus-host disease; contrast media

Case reports

Case 1

A 49-year-old patient underwent allogeneic BMT from his HLA-identical brother for AML M4 in first CR. He received GVHD prophylaxis with CsA beginning with 10 mg/kg/day, adjusted to provide serum levels of 150–250 µg/l, Mtx (15 mg/m² on day 1 and 10 mg/m² on days 3, 6 and 11), and IvIgG (0.5 g/kg/week). No serious complications occurred and rapid engraftment was achieved. Pre-existing pulmonary aspergillosis was treated with intravenous amphotericin B. Acute GVHD occurred on day +43 (grade 2, skin) without other organ involvement. The skin rash settled after 4 months. Six months after BMT the patient was still receiving CsA (5 mg/kg/day p.o.). Computed thoracoabdominal tomography was performed for evaluation of the aspergillosis infection. As contrast medium, 120 ml of iodixanolum 550 mg (Visapaque 270®) was used. Six hours after application of the contrast medium, the patient developed generalized erythroderma with a pruritic and painful skin rash. Therapy with prednisone 50 mg p.o. and cetirizin 10 mg p.o. was begun. The initial changes were limited to the more superficial skin layers, with formation of new lichen planus-like papules and scaling erythematous plaques involving facial skin, palms and soles. These findings were associated with dryness of mouth and conjunctivae. A skin biopsy showed chronic GVHD with typical epidermotropic lymphocytes characteristically surrounding keratinocytes, showing nuclear fragmentation and eosinophilic cytoplasmic degeneration ('satellitosis'). After treatment with prednisone 50 mg orally and CsA, the GVHD resolved within a few weeks.

Case 2

A 30-year-old woman with AML FAB M5b in first CR received an allogeneic BMT from her HLA-identical brother. She received GVHD prophylaxis with CsA beginning with 10 mg/kg/day, adjusted to provide serum levels of 150–250 µg/l, Mtx (15 mg/m² on day 1 and 10 mg/m² on days 3, 6 and 11), and IvIgG (0.5 g/kg/week). On day 25 post transplantation watery diarrhea occurred and a colonoscopy histologically confirmed a GVHD grade 1. Therapy with budenosid 3 × 3 mg for 20 days and initial methylprednisolone 100 mg i.v. resulted in rapid improve-

Graft-versus-host disease (GVHD) is a singularly important threat to the successful outcome of allogeneic stem cell transplantation and prevention and treatment of GVHD are of critical importance for transplant physicians and patients. Prophylactic use of cyclosporin A (CsA) and methotrexate (Mtx) successfully reduces the incidence of acute GVHD. Some studies suggest a reduction in chronic GVHD with prolonged CsA prophylaxis.^{1–3} Additional studies have shown, that random red cell transfusions given shortly before transplantation may be associated with a decreased risk of chronic GVHD, whereas unirradiated donor buffy coat or marrow reinfusions are associated with an increased risk for development of chronic GVHD.^{4,5} Splenectomy appeared to increase the risk for development of chronic GVHD, possibly due to increased rates of infection in splenectomized patients.⁶ As another possibility, which could be of prophylactic importance, we report three allogeneic BMT patients who experienced contrast media-induced cutaneous GVHD.

ment. During hospitalization computed tomography (CT) was performed and contrast medium (150 ml of iodixanolum 550 mg, Visipaque 270) was given. Two days after the CT, she developed acute cutaneous GVHD (stage 2, on day 27) which was initially treated with methylprednisolone (1000 mg/day i.v. for 4 days). Because of refractoriness, daclizumab⁷ (50 mg/day over 2 days) was added. Finally, CsA was switched to tacrolimus (1.5 mg twice a day). With this treatment the situation was stable. Almost 4 months after transplantation with no signs of GVHD (on day +110) another CT was performed when the patient was still receiving immunosuppressive therapy with tacrolimus. A total of 150 ml iodixanolum 550 mg (Visipaque 270) was given. Two hours after receiving the contrast medium the patient developed a generalized maculopapular violaceous rash over the whole body. Further therapy with methylprednisolone 1000 mg and clemastin 2 mg i.v. was initiated. Despite this treatment the rash intensified, was confluent and involved the cheeks, neck, trunk. It was associated with papule formation corresponding to grade 2 GVHD. Consequently, hospitalization occurred 18 days after the contrast medium had been given and treatment with prednisone (100 mg/day), daclizumab (50 mg/day over 2 days) and mycophenolate mofetil (2 g/day) was added to the basic immunosuppression with tacrolimus. With this treatment the skin GVHD was controlled and resolved over the next 10 weeks.

Case 3

A 38-year-old patient underwent allogeneic BMT for AML M5b from his HLA-identical brother. He received GVHD prophylaxis with CsA beginning with 10 mg/kg/day, adjusted to give serum concentrations of 150–250 µg/l, Mtx (15 mg/m² on day 1 and 10 mg/m² on days 3, 6 and 11), and IvIgG (0.5 g/kg/week). Nevertheless, he developed acute cutaneous and intestinal GVHD (grade 2, day 25) with a maculopapular rash on the hands and back, and diarrhea. With methylprednisolone (100 mg/day i.v.) the situation improved slowly. Fifteen months after the transplant the patient was not receiving any immunosuppressive therapy and a CT of the chest was performed. A total of 120 ml iopromidum 623 mg (Ultravist 300®) was given. Six hours post CT the patient developed a generalized erythrodermia which was treated with prednisone 50 mg p.o. However, the cutaneous lesions persisted. Cholestatic jaundice developed and GVHD of the skin and liver was diagnosed. Oral GVHD also developed. Since only slow improvement occurred, CsA was started again (at 5 mg/kg/day) and later mycophenolate mofetil (2 g/day) was added. In the later phase of cutaneous involvement, the patient developed a generalized poikiloderma with typical thinning of the epidermis and dermis along with teleangiectasia and reticulated pigmentation of the whole body. He still requires a continuous immunosuppressive therapy with CsA (5 mg/kg/day), mycophenolate mofetil (2 g/day) and prednisone (20 mg every other day) 1½ years after the precipitating event.

Results and discussion

Prevention of GVHD is a critical factor in transplant-related morbidity and mortality, and has been a major target of research efforts in allogeneic BMT for the past two decades. Nevertheless, some controversies still exist regarding the etiology and pathogenesis of GVHD. Therefore, many efforts have been made to distinguish different mechanisms which may influence the development of GVHD. HLA-mismatch, increasing recipient age, female donors for male patients, type of GVHD prevention, CMV positivity and others are established risk factors for the development of GVHD.⁸ With the exception of interferon- α ,⁹ drugs have never been described as triggering substances in the development of GVHD.

Reactions to contrast media

The contrast media used in our three patients were non-ionic dimers, which are supplied as iso-osmolal (290 mOsm/kg) solution. The intravenous doses are normally in the range of 50–150 ml for adults. The nonionic contrast molecules show no measurable binding to plasma proteins. They are rapidly distributed in the body and almost completely recovered unmetabolized in urine within 24 h.¹⁰ Although the newer low osmolality, nonionic contrast media are generally well tolerated and are regarded as relatively safe, reactions to contrast media are still common. There are conflicting data regarding the prevalence of delayed reactions to iodinated contrast media. Reported incidences vary from 1% to 8%. This could be due to the difficulty in verifying that adverse events occurring many hours after contrast administration are directly caused by the contrast agent.¹¹ Delayed reactions are usually defined as reactions that occur more than 1 h but within 7 days of contrast injection. Delayed reactions are usually mild. They include fever, rash, flushing, dizziness, pruritus, arthralgia, diarrhea, nausea, vomiting, headache and occasionally hypotension, and usually resolve within a few days.

Pathophysiology of reactions to contrast media

Although some reactions to the injection of iodinated contrast media are difficult to categorize, the majority of general side-effects are considered idiosyncratic or pseudo-allergic reactions. They are unpredictable, not dose-dependent, and may involve the release of histamine and other active biological mediators such as serotonin, prostaglandins, bradykinins, leukotrienes, adenosine and endothelin. There is no conclusive evidence that reactions to contrast media are allergic in nature since antibodies against contrast media could not be consistently demonstrated.¹² The delayed cutaneous reactions after contrast media administration are believed to be mediated by the deposition of immune complexes in the dermal microcirculation resulting in cutaneous vasculitis accompanied by fever. These immune complexes could trigger or precipitate cutaneous GVHD already present or latent. As in our three patients, a predisposition to GVHD was present before the contrast media again triggered it.

We believe that our three patients had GVHD and not a

delayed contrast medium reaction. In one patient we performed a skin biopsy, which showed the classical findings of GVHD. Nevertheless, one should never forget that it can be difficult to differentiate less severe histological grades of acute GVHD from drug-induced reactions. No skin biopsies were performed in cases 2 and 3 as biopsy findings correlate poorly with the clinical severity of skin rash.¹³ Although delayed reactions to non-ionic contrast media can include erythroderma, the reactions in our patients were of much longer duration than one would expect in delayed contrast media reactions, where the skin involvement disappears after a maximum duration of 7–10 days.

Another explanation for our findings could be that contrast media themselves activate a pool of antigen-specific memory T-cells in the skin, followed by cytokine secretion and expansion of the cutaneous pool of activated T-cells as well as the influx of other cell types such as eosinophils and monocytes. This action of activated cytotoxic T cells, which infiltrate the epidermis, are a well established fact in the pathogenesis of contrast media-induced delayed cutaneous reactions.¹⁴ The same mechanisms could also trigger GVHD in predisposed individuals.

In conclusion, the presence of lymphocytes and local cytokines may be of importance in transplantation tolerance and contrast media might trigger these lymphocytes. Such an alteration to the regulatory immune balance could explain the development of GVHD-like syndromes following allogeneic BMT and after administration of contrast media. To verify this hypothesis, experimental studies are required focusing on possible contrast media-induced lymphocyte activation in patients undergoing BMT.

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