



## **Graft Versus Host Disease**

### **What is Graft Versus Host Disease?**

Graft versus host disease (GVHD) is a condition which occurs after transplants, usually haematopoietic stem cell transplants but occasionally also solid organ transplants. As suggested by its name, it refers to when the "graft" (donor's cells) attack the "host" (graft recipient's cells). When the host attacks the graft is called "rejection of the graft".

GVHD can affect all the organs in the body, but the skin is the organ most frequently involved.

There are three main forms of cutaneous GVHD, acute GVHD (aGVHD), lichenoid GVHD and sclerodermoid GVHD. The last two forms are considered in the setting of chronic GVHD (cGVHD).

### **What causes Graft Versus Host Disease?**

#### ***Acute GVHD***

aGVHD most commonly occurs 4-6 weeks after the transplant, and usually within 3 months of the transplant. It is thought to be caused by a rapid growth of donor immune cells such as T-cells, natural killer cells, and soluble factors, as a reaction to the host. These donor immune cells would attack three main organs of the body, the skin, the liver and the gastrointestinal tract. The severity of symptoms in aGVHD may vary from person to person, according to the amount of damage caused to these three organs.

#### ***Chronic GVHD***

cGVHD usually begins 3 months or more after the transplant. It may progress from aGVHD but may also occur on its own in a minority of cases. The pathogenesis of cGVHD may have an autoimmune component, which is when the body produces autoantibody to fight against itself. Both T-cells and B-cells are shown to be involved in cGVHD.

### **What does Graft Versus Host Disease look like?**

#### ***Acute GVHD***

aGVHD presents in the skin as a morbilliform exanthem (meaning a red rash resembling measles, with small lesions of 2-10mm joining to form bigger lesions). It most commonly affects the hands/feet, arms, ears, chest and upper back. The lesion may concentrate more around the hair follicles, but not always. Itch is variable between patients but can be very severe. Lesions may look bruised, if the patient has low platelet counts. aGVHD is staged clinically from 1-4 according to the body surface area involved, liver involvement measured by bilirubin levels, and gastrointestinal symptoms (Table 1). Skin conditions that may mimic aGVHD include drug reactions, engraftment syndrome and viral exanthems.

## **Chronic GVHD**

Skin and mucosal involvement are common in cGVHD, and present in an early phase as lichenoid GVHD and a very late phase of sclerodermoid GVHD

Lichenoid GVHD:

- Lichen planus-like: pink to purple flat or raised small lesions with some overlying scales, often involving the back of hands/feet, forearms and trunk
- Not all patients develop this stage, and it is usually very responsive to treatment

Sclerodermatous GVHD

- Lichen sclerosis-like: red patches to large areas of thickened scar-like skin
- Morphea or scleroderma-like: deeper thickening of skin, frequently localised to traumatised areas or frictional areas
- Fasciitis: deeper skin scarring, can cause contractures, muscle aches, and impact range of motion
- Poikiloderma: pigmentary changes and increased blood vessels
- This stage could last for months and years and it is more resistant to treatment

Other manifestations:

- Oral lesions: lacey white eruption, ulcers, gingival inflammation
- Genital lesions: lacey white eruption, vaginal scarring in females, phimosis in males
- Hair: hair loss or greying
- Nails: thinning, splitting, brittleness, lifted edge, growing into finger pulp, loss of nails

## **What other problems can occur with Graft Versus Host Disease?**

### **Acute GVHD**

Other than the skin, aGVHD can damage the liver and gastrointestinal tract to cause nausea, diarrhoea, abdominal pains, deranged liver enzymes and elevated bilirubin. Table 1 outlines the clinical staging of aGVHD. Stage 4 disease confers a very poor prognosis.

Table 1: Clinical staging of acute GVHD

|         | <b><i>Skin</i></b>         | <b><i>Liver</i></b>  | <b><i>Gastrointestinal tract</i></b>       |
|---------|----------------------------|----------------------|--|
| Stage 1 | <25% body surface area     | Bilirubin 2-3 mg/dl  | Diarrhoea 0.5-1L/day, or persistent nausea |
| Stage 2 | 25-50% body surface area   | Bilirubin 3-6 mg/dl  | Diarrhoea 1-1.5L/day                       |
| Stage 3 | >50% body surface area     | Bilirubin 6-15 mg/dl | Diarrhoea >1.5L/day                        |
| Stage 4 | Erythroderma with blisters | Bilirubin >15 mg/dl  | Severe abdominal pains                     |

### **Chronic GVHD**

cGVHD may manifest in almost all body organs including:

- Eyes: inflamed eyes or eyelids, dry eyes
- Salivary gland: dry mouth
- Lungs: inflamed airways causing breathing difficulties
- Oesophagus: strictures
- Liver: blockage of bile flow
- Pancreas: enzyme deficiency
- Heart: heart rhythm problems or enlarged heart
- Nerves: sensory or motor problems

- Kidneys: increased protein excretion (nephrotic syndrome)
- Muscles: muscle cramps and weakness

### **How is Graft Versus Host Disease diagnosed?**

The diagnosis is usually made clinically by a dermatologist or a haematologist. A skin biopsy is sometimes required to rule out other diagnosis. Blood tests and imaging may be required to further investigate the other organs involved in GVHD.

### **How is Graft Versus Host Disease treated?**

After a transplant, GVHD may be partially prevented with the use of immunosuppressive medications, including cyclosporin, methotrexate, mycophenolate, tacrolimus, sirolimus, cyclophosphamide and prednisolone. These medications are usually started by the patient's haematologist. Patients should be warned regarding the symptoms of GVHD and inform their doctor when they develop any. Earlier treatment may improve the course of GVHD.

#### **Acute GVHD**

Mild skin-limited aGVHD may be treated with topical steroids. However, most patients will require stronger, systemic medications including one or more of:

- Steroids e.g. prednisolone, methylprednisolone
- Tacrolimus
- Cyclosporine
- Mycophenolate mofetil
- Methotrexate
- Biologics

#### **Chronic GVHD**

When a patient develops cGVHD, he/she is best managed by a multi-disciplinary team in a tertiary hospital. Specialists that may be involved includes haematologists, dermatologist, psychiatrist, ophthalmologists, oral medicine specialists, gastroenterologist, cardiologist, respiratory doctors and gynaecologists, depending on the patient's symptoms. Allied health staff such as physiotherapists are also helpful. Ongoing follow-up should be arranged.

Lichenoid GVHD usually responds to systemics steroids and rarely more potent treatment is needed. On the other hand, sclerodermoid GVHD is more challenging to treat. Treatment often depends on the specific symptoms experienced by the patient, and efficacy of the treatments vary significantly between patients. Some of the treatment options include:

- Steroids e.g. prednisolone, methylprednisolone
- Mycophenolate mofetil
- Methotrexate
- Azathioprine
- Hydroxychloroquine
- Acitretin
- UV therapy esp. UVA
- Rituximab
- Imatinib
- Ibrutinib
- JAK inhibitors
- Extracorporeal photophoresis

## What is the likely outcome of Graft Versus Host Disease?

GVHD is a double-edged sword. Its presence is associated with a decreased risk of malignancy relapse, but on the other hand, it can also lead to significant morbidity and mortality. Factors leading to a poorer prognosis in GVHD include a history of progressive involvement from acute to chronic GVHD, low platelets, high bilirubin, older age, gastrointestinal symptoms and lack of response to therapy. Sclerodermatous GVHD is often very persistent and challenging to treat, requiring multiple treatment options to be trialled.

### Reference:

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