HEMORRHAGIC CYSTITIS AFTER BONE MARROW TRANSPLANTATION


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Summary.- OBJECTIVES: Hemorrhagic cystitis (HC) presenting with gross hematuria, bladder pain and urinary frequency develops in 13-38% of patients following bone marrow transplantation (BMT). The objective of the study was to study the characteristics of patients suffering hemorrhagic cystitis after hematopoietic stem cell transplantation in our center.

METHODS: We conducted a retrospective chart review of all patients who underwent BMT at our institution between January 1996 and August 2012. We recorded the age, sex, diagnosis, conditioning regimen, interval between BMT and development of symptoms of cystitis and treatment instituted.

RESULTS: Five hundred patients underwent BMT in the period of time studied. 52 of them developed hemorrhagic cystitis. The mean age of the affected patients was 39 years; there were 34 males and 18 females. The diagnoses include AML (n=11), ALL (n=8), CML (n=6), MDS (n=11), CLL (n=5), NHL (n=1), HD (n=5), MM (n=2), Medular aplasia (n=3). HC appeared 59.48 days after BMT. There were no differences between sexes. Mortality among the 52 patients was 51.14 % but HC was not the cause of death in any patient. Polyomaviruses were detected in the urine of 78.94 % of survivors.

CONCLUSIONS: Polyomavirus infection with BK and JC types is usually acquired in infancy and the virus remains latent in renal tissue. Immunosuppression facilitates reactivation of the renal infection and replication of the virus responsible for the clinical manifestations of HC. The differential diagnoses include other urinary infections, lithiasis, thrombocytopenia and adverse effects of pharmacological agents. The urologist plays a limited role in the management of this disease.

Keywords: Hemorrhagic cystitis. Hematopoietic stem cell transplantation. Polyomavirus.

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Resumen.- OBJETIVOS: Tras trasplante alogénico de células hematopoyéticas aparece cistitis hemorrágica en 13-38% de casos, siendo los síntomas más frecuentes hematuria macroscópica con/sin coágulos, polaquiuria, dolor y espasmos vesicales.

Estudiar las características de los pacientes que sufren cistitis hemorrágica tras trasplante de progenitores hematopoéticos en nuestro centro.

MÉTODOS: 500 pacientes recibieron trasplante alogénico de progenitores hematopoyéticos (TAPH) entre enero de 1996 y agosto de 2012, de los cuales 52
Haemorrhagic cystitis (HC) is closely associated with allogeneic haematopoietic stem cell transplantation and develops in 13 to 38 % of the cases (1). The manifestations of HC include gross haematuria (frequently with clots), urinary frequency, dysuria, suprapubic pain and bladder spasms. Occasionally clot retention and renal insufficiency develop (2).

Haematuria that develops early is often caused by damage to the bladder epithelium by the drugs used for induction such as cyclophosphamide and busulfan and is usually self-limiting. When the symptoms develop after the graft has taken, replication of polyomavirus appears to play an important role. In these cases the symptoms tend to be more severe and haematuria can be life-threatening.

In the present study we review our experience with HC especially looking at the symptoms, aetiology and treatment.

**MATERIALS AND METHODS**

We conducted a retrospective chart review of all patients who underwent BMT at our institution between January 1996 and August 2012. We recorded the age, sex, diagnosis conditioning regimen, type of transplantation, interval between BMT and development of symptoms of cystitis, symptoms present, severity of the HC and treatment instituted.

The severity of HC was graded as follows (3):

- **Grade 1.** Microscopic haematuria.
- **Grade 2.** Gross haematuria.
- **Grade 3.** Gross haematuria with clots.
- **Grade 4.** Gross haematuria with clots and renal insufficiency secondary to obstruction.

Urine samples of patients with suspected HC were examined for the presence of viral particles by electron microscopy at the Centro Nacional de Microbiología de Majadahonda (Madrid, Spain). Virus was considered to be present when 45 nm icosahedral particles were identified in the nuclei of urothelial cell and or when viral DNA was detected by PCR.

Statistical analysis was conducted using the Student t test and Fisher’s exact test. A p value <0.05 was considered significant.

**RESULTS**

A summary of the main characteristics of the series is set on Table I.

Five hundred patients underwent BMT during the study period. Of these 52 (34 male, 18 female) with a mean age of 39.44 years developed HC. The diagnosis leading to BMT were acute myeloid leukaemia (AML) in 11 patients, acute lymphocytic leukaemia (ALL) in 8, chronic myeloid leukaemia in 6, chronic lymphocytic leukaemia in 5, myelodysplastic syndrome in 11, non-Hodgkin lymphoma in 1, Hodgkin’s disease in 5, multiple myeloma in 2 and bone marrow aplasia in 3.

There were 28 allogeneic transplantations from related donors, 17 from unrelated donors and 7 from umbilical cord cells. In 4 cases there was an HLA mismatch. The conditioning regime was the same in men and women (p=0.7541). Cyclophosphamide was used in 27 of the 52 cases and simultaneous total body radiation in 8.
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The predominant clinical presentation consisted of urinary frequency, dysuria, bladder spasms, tenesmus and micro or gross haematuria. The severity of HC was grade 1 in 7 patients, grade 2 in 27, grade 3 in 10 and grade 4 in none. Only 33% of patients had signs of urinary obstruction. Symptoms of HC started at a mean of 59.48 (range 1 to 269) days after BMT. There were no differences between men and women (p=0.802).

An urological consultation was requested in 6 of 26 males and 2 of 17 women mainly because of pain or severe haematuria. A 41.17% of men and a 61.11% of women died but the cause of death was never HC. The follow up time for was 57.47 days (range 3-136).

Blood transfusions for severe anaemia were required in 46.66% of affected men and 18.18% of women. There was a statistically significant difference (p=0002) in the incidence of massive bleeding between patients who survived and those who did not (Figure 1). Although survivors had more time free of bleeding (6.1± SD 13.89 days) than non-survivors (3.84± SD 5.58 days), the difference was not significant (p=0.4613).

Viruses were identified in the urine samples of 78.94% of surviving patients. Polyomavirus was found in 31 cases (60%), cytomegalovirus was identified in 1 case and in another patient both polyomavirus JC and adenovirus were found.

No virus was identified by electron microscopy in 9 patients (17.3%). In 7 of these patients the conditioning regime had included cyclophosphamide, in 5 busulfan and in 4 cases both drugs were used. One patient in whom no virus was found had a severe coagulopathy related to the original disease. These data are summarized in Table II. The suspected aethiological agents on each case are explained in Table III.

The mean time of onset of symptoms was 54 days post BMT in patients in whom the presence of a virus in the urine was not documented versus those in whom polyomavirus was found (mean 73 days) a difference not statistically significant (p=0.4837). Figure 2 shows the difference in symptoms between patients with confirmed virus in the urine and those without. Patients with virus in the urine had more

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Table I. Summary of the most important characteristics of the series.

<table>
<thead>
<tr>
<th>Haemorrhagic Cystitis</th>
<th>Male</th>
<th>Female</th>
<th>Signification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>39,34 years (19-66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>34/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>27 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body irradiation</td>
<td>8 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical course Grade 1</td>
<td>7 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>27 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>10 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>38,46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive virus in urine</td>
<td>38 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>51,14%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table II. Haemorrhagic cystitis' characteristics in male and female patients.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Signification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median symptoms’ beginning time</td>
<td>56.21 days</td>
<td>60.25 days</td>
<td>p=0,802</td>
</tr>
<tr>
<td>Urologist’s opinion asked</td>
<td>6</td>
<td>2</td>
<td>p=0,698</td>
</tr>
<tr>
<td>Mortality</td>
<td>14 (41.17%)</td>
<td>11 (61,11%)</td>
<td>p=0,245</td>
</tr>
<tr>
<td>Platelets transfusion</td>
<td>7</td>
<td>7</td>
<td>p=0,196</td>
</tr>
<tr>
<td>Red cells transfusion</td>
<td>16</td>
<td>3</td>
<td>p=0,037</td>
</tr>
</tbody>
</table>
frequency and tenesmus vesicae but no differences in other manifestations of HC.

The severity of the symptoms was equal in both sexes (p=0.2077). Comparing survivors and non-survivors, there were no differences between the groups in the presence of virus in the urine (p=0.6906), the severity of the disease (p=0.2765), or the number of days without bleeding (p=0.4613). Regarding time without bleeding, we found no differences between the presence and absence of virus in the urine either in survivors (p=0.9845) or non-survivors (p=0.3736).

The most commonly used treatments for HC were: hyper hydration, bladder catheter drainage with or without irrigation, platelet transfusion, anticholinergic medications (tolterodine, oxybutynin), antiseptics and antibiotics (ciprofloxacin, amoxicillin) and morphine chloride. Six patients received intravesical cidofovir.

**DISCUSSION**

The aetiology of HC can be divided into 2 categories, one is related to conditioning regime (drug induced and actinic) and viral. Drugs that can cause HC include cytostatic agents, among others cyclophosphamide, Ifosfamide, busulfan and etoposide. The other aetiologic agents are viruses, mainly polyomavirus, adenovirus (usually type 11, prevalent in Japan) and rarely cytomegalovirus.

Polyomaviruses consist of small double stranded DNA viral particles without an envelope belonging to the family of Papoviridae (4) and are the most frequent cause of HC. The first infection occurs in childhood, at the age of 3 or 4 years for the BK type and 10 to 14 for the JC type (5). The route of infection is respiratory and the virus settles in the kidneys. The virus can remain dormant for many years in the kidneys, bladder mucosa, lymphatic tissue and circulating leukocytes (6). It is estimated that 80 % of the population has been infected and has antibodies against the virus (7).

Immunosuppression facilitates the reactivation of the virus in the kidneys as can be seen in immunodeficiency, pregnancy and following organ transplantation (1). The excretion of the virus in the urine (viruria) is associated with ureteral stenosis, interstitial nephritis and graft failure after renal transplantation as well as haemorrhagic cystitis after BMT (8). In HC, viruria precedes viremia but viremia is more specific and has a greater predictive value (9). The BK virus has also been implicated y neoplasms (10) and pneumonitis (11).

The following 3 related factors play a role in the development of HC (3, 12, 13): 1) damage to the transitional urothelium during conditioning therapy; 2) massive viral replication facilitated by immunosuppression; and 3) early recovery of the immune system after transplantation.
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The development of acute graft versus host disease (GVH) and prior treatment with cyclophosphamide are considered risk factors for the development of HC (14).

Clearly, the administration of 2-mercaptoethane sulfonate (MESNA) and hyper hydration before and during the administration of cyclophosphamide have decreased the incidence of chemical cystitis caused by acrolein, an urotoxic metabolite of cyclophosphamide (15). Busulfan is also important for the development of HC and its role is increasing as the toxicity of cyclophosphamide has decreased. The simultaneous administration of both drugs increases the risk of HC (16).

GVH disease plays a facilitating role. It is postulated that viral replication in the urothelium induces expression of antigens that are detected by the newly developed immune competent cells from the donor which aggravates and perpetuates the urothelial lesion (17).

The diagnosis of HC is based on the history, the physical examination and the exclusion of other causes of painful haematuria. The differential diagnosis includes bacterial, fungal and parasitic urinary tract infections, pharmacological causes, urinary lithiasis and thrombocytopenia secondary to the primary disease or the BMT (1).

The initial treatment of HC with micro or gross is hyper hydration, forced diuresis (9, 18). If the haematuria is intense, there is suprapubic pain, or irritative voiding symptoms, a bladder catheter with continuous irrigation with normal saline solution is the usual method of treatment (8, 18). The catheter allows easier evacuation of clots and the instillation of intravesical medications (18) and is helpful to alleviate voiding discomfort and pain.

Pain medication such as morphine chloride are needed in half of the patients. Antispasmodic medications are also used often. Cystoscopy under general anaesthesia with evacuation of clots and fulguration of bleeding points is widely accepted (2).

The platelet count should be kept above $5 \times 10^4$ to minimize bleeding tendencies. Given the nature of the diseases and treatments these patients have, this may require platelet transfusion. According to the intensity of bleeding, red cell transfusion may be needed.

Have been reported in 66% of cases and partial responses in 13% (9). Since the discovery that many cases of post BMT haemorrhagic cystitis have a viral aetiology, systemic administration of antiviral medications has been used (18). Cidofovir is an acyclic nucleoside analog which has proven to have wide spectrum antiviral activity through the selective inhibition of viral DNA synthesis. It must be administered with Probenecid (9, 19). Dose dependent neurotoxicity is frequently seen with the use of Cidofovir that can be minimized using low doses (0.5 - 1 mg/kg per week) (20) or by using it for intravesical instillation (21). Complete responses of HC have been observed following Cidofovir in a 66% of patients, and partial responses in a 13% (9). Other treatments for HC have been reported in single cases or small series of patients without clear advantages over what we just discussed. They include: 1) Fibrin glue (22); 2) Intravesical hyaluronic acid (23); 3) Prostaglandin E2 bladder instillation (24); 4) Intravenous Vidarabine (25); and 5) Hyperbaric

Table III. Aetiological agents implicated in the development of haemorrhagic cystitis in the series.

<table>
<thead>
<tr>
<th>Positive virological examination</th>
<th>Coagulopathy</th>
<th>Total Body Irradiation</th>
<th>Lithiasis</th>
<th>Thrombopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyomavirus BK</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyomavirus JC</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyomavirus BK+JC</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyomavirus not specified</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus+Polyomavirus</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide +Busulfan</td>
<td>4</td>
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<td>5</td>
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<td></td>
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</tr>
<tr>
<td>Adenovirus</td>
<td>2</td>
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<td></td>
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<tr>
<td>Adenovirus+Polyomavirus</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>1</td>
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<td></td>
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<td>Cyclophosphamide +Busulfan</td>
<td>4</td>
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oxygen (26).

In our Centre, HC is usually managed by haematologists and a urologic evaluation is seldom requested. This and the fact that there are few centres where BMT is performed contribute to make HC little known in our speciality and among our colleagues. In our experience what is important in the care of these patients is to maintain good bladder drainage, evacuate clots and provide appropriate analgesia.

**CONCLUSIONS**

Polyomaviruses BK and JC are emergent viruses that often cause an infection in childhood and remain latent in renal tissue for long periods of time. Immunosuppression facilitates reactivation and viral replication is responsible for the clinical manifestations. Haemorrhagic cystitis in patients undergoing bone marrow transplantation is difficult to manage and can cause life threatening bleeding in 46.66% of the cases.

Haemorrhagic cystitis cause by cyclophosphamide toxicity is declining in frequency thanks to the routine use of hyper hydration and MESNA. In contrast busulfan is becoming increasingly more important as an urotoxic agent.

Viral haemorrhagic cystitis appears to be related to acute graft versus host disease and is usually seen after the 40th post-transplant day. The detection of the virus and the severity of urinary symptoms such as pain, frequency and urgency are unrelated to the disease prognosis.

Although long-term sequelae of HC after renal transplantation have been described this is not the case for HC following BMT. It appears reasonable to provide long-term urologic follow-up to male patients after recovering from HC. In young males because of the possibility of urethral strictures developing after prolonged catheterization and in adults because of the likely development of urological diseases associated with aging. Urologist should improve knowledge of this disease in order to provide better care for these patients.

**REFERENCES AND RECOMMENDED READINGS**

(*of special interest, **of outstanding interest)


