The role of graft-versus-host disease in haematopoietic cell transplantation-associated glomerular disease

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Abstract

Background. Glomerular disease among haematopoietic cell transplantation recipients has been attributed to chronic graft-versus-host disease. Clinical outcomes of this population may be influenced by the haematopoietic cell transplantation conditioning regimen, donor factors and chronic graft-versus-host disease.

Methods. In this review, 95 cases of haematopoietic cell transplantation-associated glomerular disease were identified from literature review for analysis. Patient characteristics, the association of chronic graft-versus-host disease with glomerular diseases, and the impact of host and haematopoietic cell transplantation regimen on outcomes were evaluated.

Results. The median onset of glomerular disease from haematopoietic cell transplantation and from cessation of immunosuppressive agents was 15.5 and 1 month, respectively. Although chronic graft-versus-host disease was common among haematopoietic cell transplant recipients with glomerulonephritis (72%), this was no different from that observed in the overall haematopoietic cell transplantation population. Membranous nephropathy and minimal change disease are the most prevalent glomerular diseases among haematopoietic cell transplantation recipients. Chronic graft-versus-host disease, donor factors and haematopoietic cell transplant regimen did not significantly impact outcomes in this study population.

Conclusions. Pathogenic mechanisms in addition to (or other than) chronic graft-versus-host disease are likely to contribute to haematopoietic cell transplantation-associated glomerular disease. Further investigation will be required to delineate clearly the pathogenesis.

Keywords: glomerulonephritis; graft-versus-host disease; haematopoietic cell transplantation; kidney disease; proteinuria

Introduction

Kidney injury is a common complication of haematopoietic cell transplantation (HCT). Over half of those undergoing HCT experience acute kidney injury, and 15–66% subsequently develop chronic kidney disease [1,2]. HCT-related kidney dysfunction frequently arises due to haemodynamic acute kidney injury, medication or contrast-induced nephrotoxicity, radiation nephritis, or thrombotic microangiopathy [2]. Glomerulonephritis, with or without nephrotic syndrome, is an important cause of kidney disease in HCT patients. HCT-related glomerulonephritis generally presents with proteinuria and may be associated with compromised glomerular filtration rate depending on the glomerular pathology. Membranous nephropathy (MGN) [3–32] and minimal change disease (MCD) [6,13,19,21–23,29,30,33–40] are the predominant findings on renal biopsy. Less common are focal segmental glomerulosclerosis (FSGS) [23,30,35,41,42], proliferative glomerulonephritis [20,25,43–45], anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis [46] and IgA nephropathy (IgAN) [47–50].

Although over half of HCT recipients have microalbuminuria during their post-transplant course [51], overt proteinuria is quite uncommon. Cohort studies have reported 4–15% with proteinuria [51,52], 0.3–8% with nephrotic-range proteinuria [21,22,30,53] and 0.2–2.4% with glomerular disease [18,21,22,53] among subjects who undergo HCT. Despite the relatively small numbers, the cumulative incidence rate of glomerular disease among HCT recipients (1–6% over variable periods, 1–10 years) far exceeds the annual rate of the general population (estimated at 0.001–0.017%) [18,22,53,54]. Glomerular disease in allogeneic HCT generally has been attributed to chronic graft-versus-host disease (GVHD) [17]. Chronic GVHD may precipitate glomerular disease after HCT via a complex donor T cell and host antigen-presenting cell interaction. Alternatively, experimental models also suggest that donor stem cells may modulate disease activity of glomerulonephritis in transplant recipients by means other than GVHD [55,56].

Donor factors and conditioning regimen seem to influence the risk of acute and chronic kidney disease [1,18,51]. Whether such HCT factors contribute to the development of glomerulonephritis remains unclear. Thus far, observa-
Table 1. Patient and transplant characteristics

<table>
<thead>
<tr>
<th></th>
<th>MGN (n = 61)</th>
<th>MCD (n = 18)</th>
<th>Other GN (n = 16)</th>
<th>All (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases (%)</td>
<td>64</td>
<td>19</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 (41 ± 16)</td>
<td>43 (38 ± 17)</td>
<td>36 (37 ± 19)</td>
<td>44 (40 ± 16)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>70*</td>
<td>44**</td>
<td>88</td>
<td>68</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>8.4 (11.4 ± 8.0)</td>
<td>13.0 (12.0 ± 7.3)</td>
<td>6.7 (8.8 ± 7.2)</td>
<td>8.4 (11.0 ± 7.7)</td>
</tr>
<tr>
<td>Autologous HCT (%)</td>
<td>3**</td>
<td>6</td>
<td>19**</td>
<td>6</td>
</tr>
<tr>
<td>Onset from HCT (months)</td>
<td>17.5 (22.1 ± 19.3)</td>
<td>11.0 (21.4 ± 25.8)</td>
<td>12.0 (27.4 ± 41.3)</td>
<td>15.5 (22.9 ± 25.2)</td>
</tr>
<tr>
<td>Onset from cessation of immunosuppression (months)</td>
<td>1.5 (3.2 ± 3.3)</td>
<td>1.0 (2.3 ± 3.2)</td>
<td>1.0 (6.7 ± 11.1)</td>
<td>1.0 (3.7 ± 6.0)</td>
</tr>
<tr>
<td>GVHD at NS onset (%)</td>
<td>75</td>
<td>69</td>
<td>58</td>
<td>72</td>
</tr>
<tr>
<td>ANA positive (%)</td>
<td>28</td>
<td>80</td>
<td>14</td>
<td>33</td>
</tr>
<tr>
<td>Unrelated HCT (%)</td>
<td>14</td>
<td>27</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>PBST (%)</td>
<td>65</td>
<td>62</td>
<td>47</td>
<td>61</td>
</tr>
<tr>
<td>Non-myeloablative or RIC (%)</td>
<td>34</td>
<td>50</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution (%)</td>
<td>66</td>
<td>73</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Death (%)</td>
<td>12</td>
<td>19</td>
<td>7</td>
<td>13</td>
</tr>
</tbody>
</table>

Values are reported as percentages or medians (mean ± standard deviation). Percentages are of known cases only.

*Comparison among allogeneic HCT recipients only (n = 89).

P = 0.023.

**P = 0.025 for comparison of MGN vs. Other GN, OR 6.81 (95% CI 1.03–45.0).


tional studies suggest that proteinuria is greater among those who undergo allogeneic HCT [52], PBST [21] and non-myeloablative HCT [18]. The rarity of the complication and the highly variable presentations make this particular question difficult to study. This study will examine the current literature to characterize further patients with HCT-associated glomerular disease in a pooled analysis and will explore the relationship of HCT treatment modality with glomerular disease.

Materials and methods

Pooled analysis of reported cases

Ninety-five subjects with HCT-related glomerular disease from case reports were pooled for analysis (Supplementary Table S1). Databases searched included MEDLINE, EBM and Cochrane collaboration. The keywords used were [Proteinuria or Nephrotic syndrome or Glomerulonephritis] ‘and’ [Bone marrow transplant (or transplantation) or Graft-versus-host disease or Hematopoietic (or Stem) cell transplant (or transplantation)]. Bibliographies of selected papers were also examined. All cases reporting glomerular pathology among HCT recipients were selected for review. Publications in languages other than English were excluded, resulting in 95 cases (from 52 publications) included in the following analysis.

Extraction of data and analysis

Demographic information, HCT type and donor factors (allogeneic vs. autologous, related vs. unrelated, myeloablative vs. non-myeloablative or reduced intensity conditioning, and BMT vs. PBST) were collected from the data when available in the published reports. GVHD-associated factors including time to onset of glomerular disease after HCT (Onset after HCT), duration of immunosuppression cessation prior to onset of disease (Duration of Immunosup), presence of acute or chronic GVHD at onset (GVHD), and anti-nuclear antibody (ANA) were evaluated. Outcomes assessed included peak level of proteinuria (Proteinuria), resolution of kidney disease (Resolution) as defined by reduction to non-nephrotic-range proteinuria or creatinine fall >50% (where kidney disease was predominantly characterized by acute kidney injury), and death. Subject data were evaluated according to glomerular disease category: MGN, MCD and other glomerulonephritis (Other GN). Patient outcomes were also assessed according to their pre-HCT conditioning regimen, HCT type and donor characteristics. Mean values were compared with t-test analysis. Non-parametric data were compared using median values and the Mann–Whitney test. Proportions were assessed using chi-square test.

Results

Patient characteristics and glomerular pathology

Mean age at onset was 40 years with a slight male predilection of 68%. Male predominance was most apparent among those with Other GN at 88%. Median daily proteinuria was 8.4 g. Membranous nephropathy was the predominant cause of glomerular pathology, comprising 64% of all reported cases (Table 1). Minimal change disease followed at 19%, and the remaining 17% were due to other glomerular diseases including FSGS (5%), proliferative GN (4%), mesangial proliferative GN (1%), ANCA-associated pauci-immune GN (1%) and IgAN (5%).

Transplant-related characteristics

Over half (61%) with glomerular disease and known HCT modality had undergone PBST rather than BMT (Table 1). Among allogeneic HCT recipients only, a greater proportion of patients with MGN (OR 3.86, P = 0.04) had PBST (known risk factor for acute and chronic GVHD [57]) performed compared with those with Other GN. All HCT recipients with glomerular disease undergoing non-
GVHD in HCT-associated glomerular disease

Table 2. Relationship of GVHD with donor factors and HCT conditioning regimen among allogeneic HCT recipients with glomerular disease

<table>
<thead>
<tr>
<th>Conditioning Regimen</th>
<th>GHVD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMT</td>
<td>48</td>
</tr>
<tr>
<td>PBST</td>
<td>71</td>
</tr>
<tr>
<td>Related HCT</td>
<td>59</td>
</tr>
<tr>
<td>Unrelated HCT</td>
<td>88</td>
</tr>
<tr>
<td>Myeloablative</td>
<td>60</td>
</tr>
<tr>
<td>Non-myeloablative</td>
<td>87</td>
</tr>
</tbody>
</table>

Percentages are of known cases only.

BMT, bone marrow transplantation; HCT, haematopoietic cell transplantation; GVHD, graft-versus-host disease; PBST, peripheral blood stem cell transplantation.

myeloablative or reduced intensity conditioning (mean age 52 + 10) were significantly older than those who received myeloablative conditioning (mean age 38 + 16, P = 0.002) as seen in the general HCT population [1]. A considerable number of autologous HCT recipients also developed glomerular disease [30,43,44,49]. Six percent of all patients with glomerulonephritis after HCT in the pooled analysis underwent autologous HCT (Table 1). Glomerular disease often presented after tapering immunosuppressive therapy a median duration of 1 month. Nevertheless, 40% of subjects developed glomerular disease while on immunosuppression. Median onset was 15.5 months from HCT, which is about the time recipient immune reconstitution occurs. These values did not differ by type of HCT (BMT vs. PBST) or by conditioning regimen (data not shown). As shown in Table 1, concomitant GVHD (72%) was common among allogeneic HCT recipients with glomerular disease, which is similar to findings in the overall HCT population (40–70%) [58]. The presence or type of GVHD is reported variably, where onset of GVHD with respect to HCT was not clearly stated in many reports. However, all those with reported GVHD at the time of glomerular disease onset had GVHD for at least 100 days. The prolonged median onset of glomerular disease (15.5 months) implies that the associated GVHD was chronic when present. Chronic GVHD association with unrelated PBST and non-myeloablative or reduced intensity conditioning is reported among HCT recipients with chronic kidney disease [51]. Though not statistically significant, chronic GVHD was greater among those with unrelated PBST and non-myeloablative or reduced intensity conditioning (Table 2). Chronic GVHD also tended to be more prevalent among patients with MGN and MCD as compared with the Other GN group (Table 1). ANA was also assessed given its association in murine GVHD. The current review found that 36% (10 of 28) tested for ANA had a positive result. Forty-seven percent of patients with chronic GVHD had presence of ANA, whereas 13% without chronic GVHD tested positive for ANA. Statistical analysis is likely limited by small sample size.

Outcomes

On the whole, reported survival rates were favorable for those who developed glomerulonephritis after HCT. Overall survival was 87%, and remission of kidney disease occurred in 70% of subjects, where median follow-up was 12 months (range: 1–96 months). The primary cause of death was end-stage renal disease, sepsis or original disease progression. Kidney disease persisted among all patients who died. Among the subgroups, 19% of MGN patients died compared with 12% of MGN patients and 7% in Other GN group. Additionally, resolution of proteinuria tended to be greatest in the Other GN group (80%) compared with MGN (66%) or MCD (73%). Neither mortality nor renal recovery differed statistically among the forms of glomerular pathology.

The presence of GVHD did not alter mortality, which was 15% and 13% among those with and without GVHD, respectively. Similarly, kidney disease resolution did not differ significantly among those with GVHD (65%) and those without GVHD (76%). HCT type (PBST vs. BMT) had no impact on outcomes of death (14% vs. 11%) or disease resolution (73% vs. 74%) in this group. Survival among HCT recipients with glomerular disease who received non-myeloablative or reduced intensity conditioning was 77%, slightly lower than those who had myeloablative conditioning (87%). Resolution of kidney disease was 27% with myeloablative conditioning and 36% with non-myeloablative regimens, but this did not achieve statistical significance. Mortality tended to be lower among subjects with late-onset disease (>6 months) in comparison with those who presented earlier (11% and 23%, respectively), though not statistically significant given the low prevalence (15%) of earlier-onset disease (<6 months).

Discussion

GVHD- and HCT-associated glomerular disease

Chronic GVHD has been implicated as the cause of glomerular pathology in most reported cases. Chronic GVHD is differentiated from acute GVHD by disease onset occurring after 100 days from HCT, with clinical manifestations of rash, diarrhea, abnormal liver function tests, bronchiolitis or microangiopathic thrombocytopenia [59]. In acute GVHD, the conditioning treatment prior to HCT damages tissues (such as the gastrointestinal tract) and stimulates pro-inflammatory cytokine production. This leads to an increased number of host antigen-presenting cells and the expansion of immunocompetent mature donor T cells, which recognize the host. Cell damage further propagates immune stimulation and the inflammatory cycle observed with GVHD [60]. The precise pathogenic mechanism differentiating chronic GVHD from acute GVHD is largely unknown due to suboptimal experimental models.

Acute GVHD is not likely implicated in the development of glomerular disease given its late presentation. Whether chronic GVHD is a determinant for glomerulonephritis in this group is not known and continues to be debated. Although the incidence of chronic GVHD is high (40–70%) among HCT recipients [58], only a small fraction of HCT recipients with chronic GVHD (1.8–5.7%) develop nephrotic syndrome [21,22,53], which is no different...
from that of the general HCT population (0.3–8%) [21,22,30,53]. In this pooled analysis, chronic GVHD is present in 72% of allogeneic HCT recipients with glomerular disease, which is comparable to the overall HCT population (40–70%) [58]. The most recent review by Brukamp et al. asserts that nephrotic syndrome was associated with chronic GVHD among 46 subjects due to the strong correlation between chronic GVHD and duration of nephrotic syndrome onset from HCT, temporal proximity of immunosuppression cessation (‘medication change’) and nephrotic syndrome, as well as concomitant presence of GVHD and nephrotic syndrome. In the current pooled analysis (which assessed 95 patients), comparisons of duration of glomerular disease onset from HCT, duration of disease onset from cessation of immunosuppression, and the presence of GVHD with respect to glomerular pathology were essentially no different than that of Brukamp et al. and did not reach statistical significance notwithstanding the larger pool of cases. Although the temporal relationship of immunosuppression cessation was only 1 month from glomerular disease onset, a substantial percentage of patients (40%) still developed glomerulonephritis while on immunosuppressive medications. Moreover, nearly a third of patients were diagnosed with glomerular disease in the absence of concomitant chronic GVHD. Unfortunately, a retrospective analysis of pooled case reports cannot examine whether GVHD is associated with the development of glomerular disease due to the lack of a comparative control group. As discussed above, comparison to a historical cohort of all-comers (all HCT recipients) suggests that GVHD is equally present in both groups.

Nonetheless, the prevailing hypothesis for glomerular pathology in the literature remains chronic GVHD. This may be primarily driven by animal studies. Specifically, MGN and MCD have been most frequently attributed to chronic GVHD. In murine models of GVHD, kidney involvement is a common manifestation of chronic graft-versus-host reaction. The typical pathological findings include mesangial proliferation with mesangial and subepithelial IgM and IgG deposits. Subendothelial immune deposits are less frequent. The features are very much like those of human lupus nephritis, and findings often include autoantibodies such as anti-DNA antibody [60]. Human chronic GVHD differs significantly from murine models, in that human chronic GVHD rarely presents as glomerular disease and no association with autoantibodies has been established. The current review corroborates the finding that ANA was not highly associated with chronic GVHD or particular glomerular disease group (Table 1).

Although some donor factors or conditioning regimens are risk factors for acute and chronic GVHD, their impact on the incidence of glomerular disease is unknown. With PBST, higher occurrence of acute and chronic GVHD may be explained by increased exposure to more mature immunocompetent T cells transfused during PBST [57]. If we believe that chronic GVHD predisposes patients to select glomerular diseases (such as MGN and MCD), then the increased incidence of glomerulonephritis among PBST recipients would be expected [57]. Modality choice of PBST may increase the likelihood of glomerular pathology, whereby in one small retrospective review of 279 consecutive patients, 24% of PBST recipients versus 3% of BMT recipients (albeit only a total of six subjects) had glomerular disease (P = 0.004) [21]. In contrast, GVHD was not significantly associated with PBST in the current pooled analysis of HCT recipients with glomerular disease where these data were available. The apparent association of PBST with glomerular disease in case reports may be reflective of the shift in modality choice from BMT to PBST in recent years and the greater recognition of glomerular disease as a cause for proteinuria.

In non-myeloablative and reduced intensity conditioning, acute GVHD is delayed or decreased, but is accompanied by higher rates of subsequent chronic GVHD. The milder conditioning regimen induces less early tissue damage, possibly allowing for reduced acute GVHD. However, greater alloimmunity in the setting of persistent mixed chimerism with reduced intensity conditioning may explain the increased chronic GVHD [61]. Investigators from the National Institutes of Health report a higher incidence of nephrotic syndrome with non-myeloablative HCT compared with myeloablative HCT. Seven of 163 consecutive patients undergoing non-myeloablative HCT developed nephrotic syndrome, whereas no incident case of nephrotic syndrome was reported in the myeloablative HCT cohort during the corresponding period. The authors ascribed the increased risk of disease to either the practice of rapid tapering of immunosuppressive therapy or persistent host antigen-presenting cells in non-myeloablative HCT [18]. However, they did not find a greater association of GVHD with glomerular disease in this select population [18]. Pre-transplant factors such as older age and greater co-morbidity may predispose to glomerular disease.

Autologous HCT recipients also develop glomerular disease [30,43,44,49]. As GVHD cannot explain the development of glomerular disease among autologous HCT recipients, any immune dysregulation or injury from HCT or related conditioning regimen probably accounts for this observation.

Alternatively, haematopoietic cells may modulate disease activity as seen in a murine model with severe IgAN that showed attenuation of the severity of the glomerular pathology after HCT from a strain with no disease and, conversely, showed worsening of glomerular injury after transplantation of bone marrow cells from mice with aggressive ‘early-onset’ IgAN to a disease ‘quiescent’ group [62]. Disease attenuation has also been reported in humans undergoing transplantation [62]. Lastly, glomerulonephritis may originate de novo unrelated to HCT-associated GVHD or to HCT itself.

Remission of kidney disease and survival

Overall prognosis was good and did not clearly differ according to pathologic diagnosis or GVHD activity in this study. HCT recipients who developed glomerulonephritis also tended to have late-onset disease, which may be due to an inherent survival advantage. This may account for the favorable remission and mortality rates. In fact, Japanese HCT recipients with late-onset (>180 days) of non-specific
kidney disease were found to have the best prognosis regardless of etiology with the survival rate highest among those with late-onset disease (87%) compared with those who presented within 120 days of HCT (47%) [53]. Better prognosis in the late-onset disease group may be due to selection bias with patients in poorer health presenting and dying sooner. Other investigators found that early-onset and middle-onset patients died most frequently due to GVHD-related pathology as opposed to late-onset patients who died due to other reasons [53].

Additionally, HCT modality or conditioning treatment did not significantly alter remission or survival in this pooled analysis, though more patients who had myeloablative conditioning, autologous HCT, BMT and late-onset kidney disease were alive at follow-up. In the general HCT population, epidemiological studies have shown age, prior acute kidney injury, prior autologous HCT, TBI, long-term calcineurin use, unrelated donor and chronic GVHD to be risk factors for non-specific chronic kidney disease [63–65]. Donor factors and conditioning regimen have also been shown to influence the risk of acute and chronic kidney disease, where the cumulative incidence rate for chronic kidney disease was two times greater among unrelated allogeneic HCT recipients compared with autologous or matched sibling allogeneic HCT recipients [64,65]. Non-myeloablative allogeneic HCT was associated with lower mortality in comparison with myeloablative allogeneic HCT despite its greater association with primary disease relapse, proteinuria, chronic kidney disease and chronic GVHD [66]. Srinivasan et al. reported non-myeloablative HCT as a risk factor for nephrotic syndrome [18]. Thus far, observational studies suggest that proteinuria is greater among those who undergo allogeneic HCT [52], PBST [21] and non-myeloablative HCT [18]. Table 3 summarizes these findings. Clearly, the small number of patients assessed in all of these studies including this pooled analysis limits analysis. Furthermore, the comparative results of this study must be interpreted with caution since the data are collected from different sources and have many potential biases (due to missing data, inconsistent definitions of variables, differing duration of follow-up, etc.). Controlled studies will likely lead to clearer conclusions.

**Diagnosis, management and therapy**

Evaluation of HCT recipients who develop overt proteinuria (with or without progressively rising creatinine) should include a renal biopsy to confirm glomerular pathology, particularly prior to initiation of immunosuppressive therapy. No randomized controlled studies have examined the optimal treatment for glomerulonephritis in this population. Treatment of glomerular diseases among HCT recipients varies but has been generally tailored to the specific glomerular pathology often including glucocorticosteroids, cyclophosphamide, cyclosporine, azathioprine, mycophenolate mofetil or rituximab [20]. Therapy has not been targeted to a particular immune system. However, treatment with immunosuppressive agents such as calcineurin inhibitors tailored to T cell inhibition and, more recently, the use of rituximab, which is more B cell specific, have been reported. Additionally, antiproteinuric agents including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and strict blood pressure control (<130/80 mmHg) according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines would be recommended. In the setting of concomitant GVHD, resumption or increase of immunosuppression (typically cyclosporine) has been used with some success [20]. With careful monitoring of kidney function (creatinine and estimated glomerular filtration rate), serum albumin and proteinuria, repeat kidney biopsy is not generally indicated as this would not likely alter management. Rarely, renal biopsy may be performed to assess for irreversible disease (extensive fibrosis) or a change in pathology (as seen in some case reports, conversion from minimal change disease to more aggressive pathology such as focal segmental glomerulosclerosis).

**Conclusions**

Glomerular disease related to HCT is a significant cause of kidney disease. Prognosis of HCT-related glomerulonephritis seems to favor survival and resolution of kidney dysfunction. The presence of chronic GVHD, donor factors or HCT regimen did not clearly impact mortality and glomerular disease resolution among HCT recipients with glomerulonephritis in this pooled analysis. MGN and MCD were the predominant glomerular pathology among HCT recipients. As chronic GVHD was not significantly associated with glomerular disease, alternative pathogenic mechanisms should be considered. Recognition of characteristic findings, clinical course and prognosis are essential
for proper management. Further insight to the mechanisms of disease will require additional animal model studies as well as clinical investigation through long-term cohort or controlled studies.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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References

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