Tubulointerstitial nephritis and cancer chemotherapy: update on a neglected clinical entity

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ABSTRACT

Background. Cancer patients are particularly vulnerable to drug-induced kidney injury during their chemotherapy. Whereas the direct nephrotoxic effects of these drugs are well recognized, that of tubulointerstitial nephritis (TIN) is less well known, underdiagnosed and often reported only as a functional tubular disorder. The diagnosis of acute TIN is important because of its insidious onset with tubular dysfunction, its potential reversibility if detected early and the possibility of its response to steroid treatment.

Methods. We performed a literature review (44 cases) and reviewed our institutional biopsy register (12 cases) of patients on cancer chemotherapy with documented TIN. Biopsies were considered in three groups: acute TIN, chronic TIN and acute on chronic TIN. The outcomes that were evaluated were recovery of kidney function, development of chronic kidney disease and onset of end-stage renal disease (ESRD).

Results. Ifosfamide, BCG, tyrosine kinase inhibitors and premetrexed were the most commonly implicated drugs. Ifosfamide and premetrexed were associated with worst outcomes. Recovery of kidney function was better in acute TIN (ATIN) (29%) with fewer progressing to ESRD (12.9%) than with chronic TIN (7.6% recovery, 15.3% ESRD). Steroid use appeared to favorably alter outcomes in ATIN (40% recovery) compared with conservative treatment (18.75% recovery). Peak serum creatinine, age, gender and type of malignancy did not influence outcomes.

Conclusions. As a potentially reversible lesion that can respond to withdrawal of the suspected agent, and in some cases to a short course of steroid therapy, it is important to consider ATIN in the differential diagnosis of all cases of acute kidney injury in cancer patients on chemotherapy.

INTRODUCTION

The prevalence of reduced kidney function is high in patients with cancer, rendering them particularly vulnerable to kidney injury during the course of their chemotherapy [1–4]. Predisposing factors such as old age (unrecognized low glomerular filtration rate, reduced total body water), comorbid conditions (diabetes, cardiovascular disease, impaired immune system) and complications of malignancy (malnutrition, hyperuricemia, hypercalcemia) often increase the risk and magnify the renal injury sustained during exposure to chemotherapeutic agents. The direct nephrotoxic effect of most anticancer drugs are well known, and precautions such as dosage adjustment, use of less nephrotoxic agents and preventive measures are well integrated into oncology practice [2–5]. Less well appreciated and underdiagnosed is renal injury due to tubulointerstitial nephritis (TIN). As a result, in its potentially reversible acute form, TIN (ATIN) often goes unrecognized as a cause of kidney injury until it progresses to an irreversible chronic form (CTIN) [6, 7]. The diagnosis of TIN is based on its clinical and laboratory manifestations, characteristic morphologic features on kidney biopsy and the identification of a causative factor, whose early removal reverses the injury and is essential to the prevention of permanent renal damage. Satisfying all of these diagnostic requirements is often fraught with limitations,
leading to an overall underdiagnosis of ATIN in general, particularly during chemotherapy of cancer patients.

Kidney biopsy specimens from patients with unexplained acute kidney injury (AKI) reveal a frequency of ATIN that ranges from 8 to 22%, higher frequencies being reported in elderly patients [6, 8]. Approximately 70–92% of ATIN cases are related to drugs, others to infectious agents and a few are idiopathic [3, 7–9]. Drugs responsible for causing TIN are primarily antibiotics, though analgesics, anticonvulsants, diuretics, antiulcer agents and other medications have been implicated [3, 6]. Anticancer drugs as a cause of ATIN are mentioned in some reviews but remain under-emphasized in textbooks and under-reported in the literature leading to the underdiagnosis of a potentially reversible renal injury [6, 7]. This update highlights the occurrence of acute and chronic TIN associated with chemotherapeutic agents, describes their clinical and morphologic features, identifies the cancer drugs commonly incriminated in their pathogenesis and assesses the role of steroid therapy in their management.

SUBJECTS AND METHODS

The first part of this study consists of a review of kidney biopsies from our institution over the period of 2000–2010 and the second part is a literature review of reported cases of chemotherapy-induced TIN. Our pathology department serves as a referral nephropathology center for two major (Methodist Hospital and Ben Taub General Hospital) and several minor Houston hospitals; it does not review biopsies from pediatric cases or the local regional cancer hospital (MD Anderson Cancer Center). Kidney biopsies from cancer cases were identified from our internal registry and those with an acute or chronic TIN attributed to a chemotherapeutic agent were selected for additional examination. All biopsies were submitted to light microscopic, immunofluorescent and electron microscopic examination. The tubulointerstitial changes were semiquantified on a scale of 0–4 for interstitial inflammatory infiltrates, fibrosis and edema (Table 1).

The second part of this study is a literature review, for which the terms cancer, chemotherapy, acute TIN, chronic TIN, acute interstitial nephritis, chronic interstitial nephritis, kidney disease, interstitial nephritis and nephrotoxicity were searched for in PubMed and Medline for the period ending December 2012. Reported cases of TIN attributed to chemotherapeutic agents were identified from a survey of published abstracts, and reprinted articles of identified cases reviewed for the following information: age, gender, race, malignancy type, presence of comorbid conditions (diabetes, COPD, congestive heart failure, stroke, coronary artery disease, infection), reported use of non-steroidal anti-inflammatory drugs (NSAIDs) or antibiotics, radiation therapy or recent contrast administration. Additionally, the following laboratory results were obtained when available: albumin, hemoglobin, hematocrit, white blood cell count (with eosinophilia), urinalysis, the baseline/peak and follow-up creatinine, kidney biopsy results and the specific treatment for the TIN (steroids or dialysis). Few reports provided all the information considered useful to abstract.

Cases were classified into: acute TIN, chronic TIN and acute-on-chronic TIN. A fourth category from the literature review included two cases where the diagnosis of ATIN was based on convincing clinical evidence, but a kidney biopsy was not done for a definitive diagnosis [10, 11]. Both recovered kidney function after discontinuation of chemotherapy and are included in the study as ATIN.

RESULTS

Of the 3765 kidney biopsies reviewed by our pathology department between 2000 and 2010, 243 (6.5%) biopsies were diagnosed as either acute or chronic TIN. Twelve of the 243 biopsies (4.9% of TIN cases) were from patients with a diagnosis of cancer and a chemotherapeutic agent was implicated as the cause of TIN. Of the total 3765 kidney biopsies, a co-existent diagnosis of cancer was listed in 25 cases; hence, nearly half (12 cases, 48%) of all cancer patients undergoing kidney biopsy were diagnosed as having TIN. The diagnoses of the other 13 non-TIN cases were acute tubular necrosis (five cases), infiltrating malignancy (four cases) and glomerulopathies (four cases).

Table 1 lists the clinical and biopsy features and incriminated agents in the 12 cases. The average age of the patients was 54 years (range 35–84 years). There were six females and six males. Five of the 12 patients (41.6%) were diagnosed with lymphoma. The implicated agents in the 12 cases were ifosfamide (IFO), 5 cases; doxorubicin (Adriamycin), 2 cases; carboplatin, 2 cases; the others were single cases due to diverse agents (Table 1). The average serum creatinine at the time of kidney biopsy was 5.0 mg/dL compared with 1.2 mg/dL at baseline. Long-term follow-up was available in five cases, three of whom were on hemodialysis (Table 1, cases 3, 6 and 7), and all the three had been treated with IFO. Of the other two, one (case 1) had ATIN attributed to Adriamycin, and at 3-week follow-up, the creatinine was 1.6 mg/dL; the other (case 5) had received methotrexate and his creatinine was 1.2 mg/dL at a 7-year follow-up.

Eleven of the twelve biopsies of our institutional cases were from native kidneys and one from a transplanted kidney (Table 1, case 9). Adequate tissue was available from all biopsies. There were 4–42 glomeruli in each biopsy, most of which revealed a few globally sclerotic glomeruli. IgA nephropathy was noted in two biopsies (cases 6 and 11) and the transplant biopsy showed early transplant glomerulopathy. All of the observed glomerular lesions were mild and focal (Table 1, Figure 1), were likely of incidental nature and considered unrelated to the more prominent TIN lesions. All of the 12 biopsies showed severe tubulointerstitial injury of acute or chronic nature, leading to the diagnoses of acute, chronic or acute-on-chronic TIN (Table 1, Figure 1). The inflammatory cell infiltrates were mostly small lymphocytes and a few mature plasma cells. Eosinophils were noted in three biopsies (Table 1, cases 1, 2 and 11) but were few in number (Figure 1B). Tubular cell nuclei showed atypia in two biopsies.
Table 1. Chemotherapeutic drugs associated with TIN from a single center

<table>
<thead>
<tr>
<th>Year</th>
<th>Gender</th>
<th>Age</th>
<th>Base Cr</th>
<th>Peak Cr</th>
<th>Final Cr</th>
<th>Cancer</th>
<th>Drug</th>
<th>Glomeruli</th>
<th>Abnormal glomeruli</th>
<th>Infiltrates</th>
<th>Fibrosis</th>
<th>Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>F</td>
<td>73</td>
<td>N/A</td>
<td>3.0</td>
<td>N/A</td>
<td>BST</td>
<td>ADR</td>
<td>31</td>
<td>3 GS</td>
<td>3+</td>
<td>0</td>
<td>1+</td>
</tr>
<tr>
<td>2006</td>
<td>F</td>
<td>76</td>
<td>1.4</td>
<td>7.0</td>
<td>1.6</td>
<td>LUN</td>
<td>CP</td>
<td>7</td>
<td>0</td>
<td>3+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>2011</td>
<td>F</td>
<td>46</td>
<td>52</td>
<td>10.0</td>
<td>N/A</td>
<td>LYM</td>
<td>IFO</td>
<td>9</td>
<td>0</td>
<td>3+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>2012</td>
<td>F</td>
<td>52</td>
<td>35</td>
<td>4.0</td>
<td>N/A</td>
<td>LYM</td>
<td>IFO</td>
<td>42</td>
<td>3 GS</td>
<td>2+</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>2005</td>
<td>F</td>
<td>35</td>
<td>43</td>
<td>2.2</td>
<td>1.2</td>
<td>LYM</td>
<td>IFO</td>
<td>38</td>
<td>12 GS</td>
<td>3+</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>2010</td>
<td>M</td>
<td>43</td>
<td>54</td>
<td>5.0</td>
<td>5.0</td>
<td>LYM</td>
<td>MTX</td>
<td>38</td>
<td>1 GS</td>
<td>1+</td>
<td>3+</td>
<td>3+</td>
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<tr>
<td>2011</td>
<td>M</td>
<td>54</td>
<td>39</td>
<td>2.0</td>
<td>6.0</td>
<td>LYM</td>
<td>IFO</td>
<td>31</td>
<td>1 GS</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>2007</td>
<td>F</td>
<td>47</td>
<td>N/A</td>
<td>2.0</td>
<td>ESRD</td>
<td>LYM</td>
<td>IFO</td>
<td>6</td>
<td>8 GS</td>
<td>3+</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>2006</td>
<td>M</td>
<td>84</td>
<td>N/A</td>
<td>2.5</td>
<td>ESRD</td>
<td>LUN</td>
<td>ADR</td>
<td>4</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>2002</td>
<td>M</td>
<td>58</td>
<td>N/A</td>
<td>1.9</td>
<td>ESRD</td>
<td>LUN</td>
<td>IFO</td>
<td>11</td>
<td>1 GS</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>2008</td>
<td>M</td>
<td>55</td>
<td>N/A</td>
<td>8.0</td>
<td>ESRD</td>
<td>CAR</td>
<td>CP</td>
<td>4</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
</tbody>
</table>

Cases of tubulointerstitial nephritis (TIN) at our institution considered to be secondary to cancer chemotherapy. Based on available information retrieved from chart review of cases diagnosed by kidney biopsy as acute TIN (ATIN), chronic TIN (CTIN) and co-existent acute and chronic TIN (ATIN and CTIN).

*aGender reported as M, Male; F, Female.*

*bAll serum creatinine levels reported in mg/dL. N/A, Not available.*

*cCancers reported as LUN (lung), LYM (lymphoma), SAR (sarcoma) and CAR (carcinoid).*

*dChemotherapeutic drugs abbreviated as follows: ifosfamide (IFO), Adriamycin (ADR), carboplatin (CP), methotrexate (MTX), gefitinib (GEF) and interferon (INF).*

*eTotal number of glomeruli on biopsy specimen.*

*fNumber of abnormal glomeruli reported as: GS, glomerular sclerosis; SS, segmental sclerosis.*

*gInterstitial cellular infiltrates, fibrosis and edema graded as: 0 = <5% cortical area; 1+ = 5–25% of cortical area; 2+ = 26–50%; 3+ = >50%; Eos = Eosinophils. Patients 6 and 10 had global, diffuse mesangial IgA deposits on immunofluorescence.*

(Tables 1; cases 4 and 9) but viral changes were not identified. In all of the cases, the blood vessels were either normal or showed mild intimal fibrosis, medial thickening or hyalinosis. The severe chronic tubulointerstitial injury in the single renal transplant biopsy (Table 1, case 9) was probably unrelated to rejection since features of acute or chronic rejection were absent. Except for the two cases of IgA nephropathy, immunofluorescence was negative in the others and electron microscopy revealed no tubular basement membrane (TBM) deposits in any of the specimens.

The literature review revealed 44 cases of TIN attributed to chemotherapeutic agents (Table 2) [10–39]. The diagnosis was acute TIN in 31 of the 44 cases (70.5%) [10–32], reflecting the general tendency to biopsy cases of unknown AKI rather than those with chronic kidney disease (CKD). Affected patients were of both genders (20 males, 11 females; with a male-to-female ratio of 1.8) and of all age groups (range 5–72 years). Fourteen of the patients were older than 65 years, eight were under 18 years and the remainder were in between (18–65 years), indicating susceptibility to TIN in all age groups. The reported cases occurred in 20 different types of malignancies (8 renal; 7 bladder; 5 lung; 4 hematologic; 3 breast; 3 Ewing’s sarcoma; 2 ovarian; 2 pancreas and the rest in varied individual tumors) and were associated with 14 different chemotherapeutic drugs (Table 2). Three of the 31 patients with ATIN were simultaneously ingesting NSAIDs, which are incriminated in causing ATIN but were not considered the cause of injury in the reports. As shown in Figure 2, 9 of the 31 (29%) cases of ATIN had full recovery of kidney function, while 4 (12.9%) progressed to end-stage renal disease (ESRD).
requiring maintenance hemodialysis. Three of the ESRD cases were due to IFO and one to IL-2. Four patients died from causes unrelated to their kidney disease; the remaining 14 (45.1%) did not improve to their baseline creatinine level at the end of follow-up and are labeled CKD in the figure. Fifteen patients with ATIN were treated with steroids (Figure 3): six of them responded with normalization of their serum creatinine (40%), one progressed to ESRD (7%) and eight had reduced residual kidney function or CKD at last reported follow-up (53%). Of those not treated with steroids, three recovered (18.7%), six developed CKD (37.5%), three progressed to ESRD (18.75%) and four expired (25%). The net increase in creatinine levels from baseline, age, gender or type of malignancy did not influence the prognosis or outcome of ATIN.

Information provided on clinical and laboratory findings was limited. Urinalysis findings were reported in 18 of the 31 (58.8%) cases of ATIN. Fourteen of the 18 cases (77.8%) had some evidence of renal dysfunction on urinalysis, such as proteinuria (14 cases), renal glycosuria (1 case), granular casts (3 cases) and leukocytes (3 cases) [10, 11, 18, 20, 26–31]. Eosinophiluria was reported in only two cases, one in association with the use of recombinant leukocyte interferon-alpha and the other with sunitinib. Peripheral eosinophilia was reported in nine cases and ranged from 1 to 40%. Skin rash was reported in six cases, three of whom were treated with tyrosine kinase inhibitors, one with sunitinib and two with sorafenib.

Chronic TIN (Table 2) was the diagnosis in 13 of the reported 44 cases [21, 33–39]. This is less than half that of reported ATIN cases and is likely a reflection of the greater tendency to biopsy cases of AKI. Seven of the 13 CTIN cases (53.8%) were reported as having features of acute and chronic TIN, probably representing the progression of ATIN to CTIN due to continued exposure to the drug or possibly pre-existing kidney disease with superimposed ATIN due to the chemotherapeutic agent as an added insult [21, 36–39]. All of these seven patients were older than 50 years; one had a prior diagnosis of CKD and the other of hypertension. Five of the 13 CTIN patients (38.4%) were treated with steroids, but only 1 patient responded with normalization of serum creatinine [36]. Of the remaining 12 CTIN patients, all experienced progressive loss of kidney function with 10 having residual CKD and 2 progressing to ESRD (Figure 2). Gender distribution (eight men and five women) in CTIN cases was almost similar to that of ATIN cases with a

FIGURE 1: Illustrative kidney biopsies of acute, chronic and acute on chronic tubulointerstitial nephritis. (A) Acute tubulointerstitial nephritis (case 2): Some tubules show acute changes including flattened tubular epithelial cells and necrotic debris in tubular lumen (box). There is no significant tubular atrophy. There is interstitial edema with mild early fibrosis and mild inflammatory cell infiltrate. The glomerulus (lower right) shows no significant changes (hematoxylin and eosin stain, ×200). (B) Acute tubulointerstitial nephritis (case 2): In another area, there is marked interstitial inflammatory cell infiltrates, with a few eosinophils (arrows) (hematoxylin and eosin stain, ×400). (C) Chronic tubulointerstitial nephritis (case 3): There is marked tubular atrophy, interstitial fibrosis and interstitial inflammation. A few intact tubular profiles remain (arrows). The glomerulus (lower right) shows no significant changes (hematoxylin and eosin, ×200). (D) Tubulointerstitial nephritis with both acute and chronic components (case 11). The chronic injury includes marked tubular atrophy, interstitial fibrosis and mild inflammatory cell infiltrates. In addition, acute changes of tubular epithelial cells are noted (boxes), including nuclear atypia, necrotic changes and detachment from basement membrane. The glomerulus (upper left) shows no significant changes ((hematoxylin and eosin stain, ×200).
male-to-female ratio of 1.6 and affected all age groups (range 13–70 years): three cases were <18 years, four were >65 years and the others between 18 and 65.

Two cases reported as ATIN were due to a hypersensitivity reaction to a chemotherapeutic agent (sunitinib, methotrexate) on the basis of clinical evidence without a kidney biopsy; both recovered kidney function after drug cessation without steroids [10, 11]. Similar cases due to chemotherapy or any other drugs are likely encountered often in clinical practice and generally go unrecorded in the literature due to lack of biopsy.

Ifosfamide, BCG, the tyrosine kinase inhibitors and premetrexed accounted for more than two-thirds (68.2%) of the cases reported in the literature (Table 2). The eleven cases of TIN attributed to ifosfamide (25% of the reported cases) resulted in irreversible kidney injury, leading to ESRD in five and CKD in six cases. In four of the ATIN cases attributed to IFO, there was improvement in kidney function but not to baseline [23, 24]. Ifosfamide was also the most common agent (5 of 12, 41.6%) in our institutional cases (Table 1), none of whom completely recovered kidney function, with three of the five progressing to ESRD. Tubular dysfunctions are a well-recognized adverse effect of IFO and are said to occur in one-third of patients who receive a cumulative dose of greater than 90 gm/m2. Only one of the cases reported in our literature review exceeded this level [34], the remainder (10 cases) occurred in individuals who received a total dose of <57 gm/m2 and in two of them at a total dose of 14 gm/m2. Of the four IFO cases treated with steroids, two progressed to ESRD and the other two improved but had residual CKD.

BCG was the second (16%) most common agent associated with TIN reported in the literature, but in none of our

Table 2. Chemotherapeutics associated with tubulointerstitial nephritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Literature review</th>
<th>Institutional cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>ATIN</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>BCG</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Premetrexel</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>IL-2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Interferon</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Chemotherapeutic agents associated with TIN from literature review (n = 44) and our institution between the years 2000 and 2010 (n = 12). ATIN, acute tubulointerstitial nephritis; CTIN, chronic tubulointerstitial nephritis; A+CTIN, acute and chronic tubulointerstitial nephritis; BCG, Bacillus Calmette-Guerin. The four drugs reported in single cases of TIN, listed as Other, were: lenalidomide, bevacizumab, recombinant leukocyte interferon-alpha and tretinoin.

**Figure 2:** Outcome of chemotherapy-associated tubulointerstitial nephritis (TIN). ATIN, acute TIN; CTIN, chronic TIN.

**Figure 3:** Effect of steroid treatment on outcome of cases of acute tubulointerstitial nephritis (ATIN) compared with those treated conservatively.
The institutional and literature reviews of this study highlight that both acute and chronic TIN account for cases of kidney injury during cancer chemotherapy. The incidence of ATIN and CTIN in such cases is most likely much higher than recorded heretofore. The vast majority of cases go unreported for several reasons: lack of kidney biopsy, adverse patient outcome, resolution of AKI upon completion or withdrawal of chemotherapy and failure to properly consider and document the diagnosis. The fact that none of the 12 cases identified in our institutional review was reported clearly documents the relative infrequency with which the recording and study of these cases are handled. The overall low number of kidney biopsies in patients with cancer (0.66% of biopsies at our institution) represents the relative infrequency with which this invasive procedure is undertaken in patients with a potentially fatal and usually serious cancer. By contrast, the diagnosis of TIN in almost half of the biopsied cancer cases from our institution suggests the relative importance of this diagnosis in cancer patients who sustain reduced kidney function during the course of their chemotherapy. The number of biopsied cases appears to be increasing as 11 of our 12 biopsies were performed after 2005. The reason for this increment is not possible to determine from this retrospective review, but may well be a reflection of the increasing awareness by nephrologists of what has come to be termed ‘onco-nephrology’ [4, 43] and the increasing number of publications addressing the issue over the past decade; for example, there were 181 PubMed hits for ‘acute renal failure and cancer’ in 2010, compared with 75 in 2000.

It is relevant in this regard that reviews on the subject of kidney injury due to chemotherapy list what are likely cases of TIN by their clinical laboratory manifestations as causing tubulopathies (salt wasting, magnesium wasting, nephrogenic diabetes insipidus) as distinct and separate from that of acute or chronic TIN [2, 43]. Indeed, the literature includes many cases of chemotherapy reported as causing Fanconi syndrome, nephrogenic diabetes insipidus and electrolyte abnormalities without mention of TIN, exploring the presence of hypersensitivity manifestations (eosinophilia, eosinophiluria, fever or rash) or considering the need for a kidney biopsy [44–46]. Clinically, the initial and most evident manifestations of TIN are those of tubular dysfunction (increased fractional excretion of sodium, inability to concentrate the urine, hyperkalemia, acidosis, phosphaturia, uricosuria). The drop in glomerular filtration rate and increase in creatinine levels may be present early in severe cases of ATIN, but usually follows that of the earlier manifestations of tubular dysfunction, which may go undetected [6, 7]. This is an important consideration not only for the early diagnosis of the potentially reversible lesions of ATIN but also for the nosology of these cases under a single entity (TIN), rather than separately by various and differing tubular dysfunctions.

ATIN due to drugs is considered an immune-mediated lesion due to a hypersensitivity reaction to the implicated agents. It is distinctly different from direct nephrotoxicity by the fact that the injury is not dose related, affects a small number of those exposed to the drug, occurs in an unrelated group of agents, is accompanied by systemic manifestations of hypersensitivity, recurs upon re-exposure to the drug, is reversible if the incriminated agent is withdrawn and appears to respond to a short course of steroid therapy [6, 7, 47]. Considered as a group, the cases reviewed in this study fulfill these criteria. The lesions were not dose related, they occurred in a relatively small group of subjects with varied tumors exposed to unrelated agents (Tables 1 and 2), they were accompanied by systemic manifestations (eosinophilia, rash), when the drug was withdrawn kidney function improved in about a third of the cases (Figure 2), where treated with steroids, 40% of ATIN cases recovered baseline kidney function compared with 18.75% in those not treated (Figure 3) and in some the lesion recurred on re-exposure [10, 36].

Overall, steroid treatment seemed to alter the outcome of ATIN favorably (Figure 3). Obviously, it is impossible to make this statement with much certainty on the basis of the results of this review, given the selective nature of the reported cases and the subjective decision to treat with steroids. However, considered in light of the increased evidence of a favorable response of ATIN to early steroid treatment [47, 48], their use deserves consideration in cases of ATIN due to chemotherapeutic agents.

**CONCLUSION**

AKI, of varied etiology, is common in cancer patients in whom it adversely affects outcomes and can be severe enough
to necessitate renal replacement therapy [1, 2, 5]. Not well recognized, often not fully explored and usually under-reported as a cause of AKI is acute TIN. As a potentially reversible lesion, which can respond to withdrawal of the suspected agent and in some cases to a short course of tapered steroid therapy, it is important to consider ATIN in the differential diagnosis of all cases of AKI in cancer patients on chemotherapy. Early detection and proper treatment can prevent its progression to CTIN with reduced residual kidney function or the need for dialysis.

CONFLICT OF INTEREST STATEMENT

The authors have no financial disclosures to divulge for the period within the 60 months preceding submission of this manuscript. M.A., R.R., L.T., G.E.: none declared.

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This interesting report highlights the association between malignancies, chemotherapy and tubulointerstitial nephritis (TIN). The authors make the valid point that acute kidney injury (AKI) in patients with cancer is most likely to be multifactorial with drug-induced TIN being an important consideration. The study also stresses the importance of renal biopsies in case of AKI of unknown aetiology, as the finding of an acute TIN is amenable to therapeutic intervention (steroids) and functional recovery. Early intervention in such case is more likely to prevent lasting scarring and fibrosis, thus preserving renal function.

Patients with malignancies can suffer AKI from a number of causes ranging from the malignant infiltration of the kidney, treatment of the cancer (chemotherapy), (electrolytes disorders (including hypercalcemia and hyperuricemia), tumor lysis syndrome (most commonly with lymphoproliferative disorders), dehydration as well as a number of concomitant potentially nephrotoxic medications including NSAIDs and PPIs as well as drug-induced crystalluria (anti-virals and antibiotics: ciprofloxacin).

Infections, bacterial but also viral (Adenovirus, EBV and BK virus induced TIN have been reported with myeloproliferative malignancies [1]) have been associated with TIN in malignancies. With that in mind, screening for viral infections would also be warranted in cancer patients who present with an acute TIN (aTIN).

The NDT ERA-EDTA OLA readers may be interested to learn more from the authors of this very interesting article about:

(1) As a significant percentage (41%) of those affected had an underlying lymphoproliferative malignancy, how can the nephrologist differentiate between drug-induced aTIN from the infiltration of the kidneys by neoplastic lymphocytic cells?

(2) Also some reports have shown an association between IgG4-related TIN and lymphomas (2). Were there excess IgG4+ plasma cells in the infiltrate of any of the patients with lymphoma and aTIN?

(3) Whether there were, in this series, susceptibility factors, such as older age or concomitant medications, which may have predisposed those treated to AKI?

(4) Recommendations regarding interventions to minimize the risk of aTIN and AKI in cancer patients receiving chemotherapy.

Prof Meguid El Nahas

REFERENCES


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ORIGINAL ARTICLE

NDT ERA-EDTA OLA has selected this publication for Blog commentary by its faculty in view of its quality and potential educational value.