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LETTERS TO THE EDITOR

Emphysematous pyelonephritis in a female with diabetes mellitus, renal calculi, breast cancer and chemotherapy-induced lymphopenia, successfully managed without nephrectomy

Dear Editor,

Emphysematous pyelonephritis (EPN) is a rare, life-threatening, gas-producing, renal and perirenal infection, commonly caused by *E. coli* or *K. pneumoniae* [1,2], more frequently affecting women of mean age of 60 years, involving one or both kidneys. Diabetes mellitus, obstruction of urine flow, and defective patient's immune response [1-3] have been recognized as predisposing factors. EPN prognosis and treatment depend on its extent and presence of risk factors, such as thrombocytopenia, acute renal failure, disturbances of consciousness or shock [1,2]. Chemotherapy-induced lymphopenia may herald febrile neutropenia and predisposes to non-neutropenic infections [4,5].

We report on the case of a 61-year-old diabetic woman with renal calculi and breast carcinoma who, after her 4th course of epirubicin/docetaxel chemotherapy, developed non-neutropenic EPN, being at a long (109-day) lymphopenic state. EPN threatened her life, while nephrectomy proved infeasible. This case, bearing many predisposing and unfavorable prognostic factors, was actually cured with antibiotics, incision drainage and nephrostomy without nephrectomy and was followed up over 5 years. The patient remained with asymptomatic pyuria/bacteriuria for 5 years with creatinine clearance 45 ml/min and her breast cancer in remission on anastrozole.

EPN is a rare type of urinary tract infection. One should suspect EPN in any case of pyelonephritis resistant to or recurring despite proper therapy in a diabetic patient [1,3], and diagnose it by the presence of gas on US or CT scan confined to the affected renal and/or perirenal structures.

Our patient remained with creatinine clearance 40 ml/min, and a 35% function of the affected kidney. Thus, nephrectomy might further reduce her renal function, due to diabetes mellitus and compromised renal tissue, making her a potentially hemodialysis-dependent subject.

Besides, risk factors such as thrombocytopenia, acute renal failure, disturbances of consciousness or shock were correlated with the outcome of extensive EPN. For localized and for extensive EPN with no or one risk factor present, percutaneous catheter drainage combined with antibiotic therapy have provided a good outcome [1,2]. For extensive EPN with more than one risk factors present, prompt nephrectomy could provide the best outcome [1,2]. Our extensive EPN case presented with 3 coexisting risk factors (increased serum creatinine levels, confusion state and shock) and poor prognosis. In our patient thrombocytopenia could represent chemotherapy-induced myelosuppression rather than an EPN-intrinsic phenomenon, as that coexisted with neutrophil count drop.

Lymphopenia (≤700/μl) on day 5 and, of lower sensitivity, on day 1 post-chemotherapy is an independent risk factor for febrile neutropenia [5]. Treatment with docetaxel-containing regimens may result in severe CD4+ lymphopenia leading to immune deficiency and increasing the risk of opportunistic and non opportunistic infections, although no non-neutropenic EPN case has been reported so far [4,5]. In all studies, the most affected subsets of lymphocytes after a single course of docetaxel monotherapy in patients with solid tumors, and as early as 7 days after administration, are, except the CD4+ lymphocytes, the CD3+, CD8+ and CD56+(NK), but not the B-cells (CD20+). In the subsequent chemotherapy courses these subsets of lymphocytes decrease even more, but also decrease the CD20+ and to a lesser degree the CD56+ subsets. It is remarkable that almost all lymphopenic patients of the series who developed non neutropenic infections had a normal level of IgG and Igm. Docetaxel-based chemotherapy discontinuance resulted in recovery and normal count of almost all lymphocyte subsets (mostly CD3+ and CD4+) within 3 months [4,5].

This case bore all the predisposing factors for EPN development, and all the unfavorable factors for survival. Delay might make nephrectomy technically impossible and chemotherapy induced-lymphopenia can prolong EPN course, causing an extra heavy clinical burden.

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Acute renal failure and multiple extranodal involvement in a patient with diffuse large B cell lymphoma

Dear Editor,

At least 25% of non-Hodgkin's lymphomas (NHLs) arise in tissue other than the lymph nodes, spleen, or the bone marrow and are referred to as primary extranodal NHLs [1]. In these cases, the most common extranodal localization are stomach, CNS, bone, testis and liver [2]. In addition to the above subtypes of NHL, there is a group of lymphomas that includes patients whose disease is diagnosed simultaneously at several extranodal sites. The majority of these cases (two or more sites) are characterized by gastric or intestinal disease localization, with or without simultaneous involvement of other extranodal sites, mainly bone or lung [3].

A 36-year-old female was admitted to our oncology department in July 2007 with fever, weight loss and oliguria. She complained of right shoulder pain and a mass which increased progressively for 1 month. After plain radiograph and MRI of the shoulder, the mass was biopsied and the result was still awaited. Initial laboratory tests were as follows: white blood cell count 9.2×10^9/l (range 4.8-10.8), hemoglobin 8.1 g/dL (range 12-15), creatinine 2.85 mg/dl (range 0.7-1.2), urea 63 mg/dl (range 10-50), lactate dehydrogenase 390 mg/dl (range 240-480). Urine output was 250 ml/day. An abdominal CT scan was normal except diffuse enlargement of both kidneys. Because of neurologic signs we performed brain MRI which revealed an intracerebellar mass. A biopsy taken from the right shoulder showed a diffuse large B-cell lymphoma. Finally, the patient was diagnosed with stage IVB diffuse large B-cell lymphoma (DLBCL) with 3 extranodal sites (both kidneys, brain, and right shoulder). She was then treated with combination chemotherapy (R-CHOP) and cranial radiotherapy. Both kidneys returned to within normal size after 3 cycles of R-CHOP. After 6 cycles of this regimen the mass in the right shoulder was almost in complete clinical remission, but the FDG-PET/CT scan showed residual disease involving both kidneys, the right shoulder and the cerebellum. After 8 cycles of R-CHOP, the patient received systemic methotrexate (3 g/m^2) with folinic acid rescue. During this treatment, the disease progressed and the patient died 7 months after the diagnosis.

NHL constitutes a group of disorders originating from malignant transformation of lymphocytes and involving either the lymph nodes or extranodal sites [4]. Noncontiguous extranodal sites at presentation without lymph node involvement is rare. Moreover, to the best of our knowledge, bilateral renal involvement in addition to bone and CNS involvement at baseline has not been reported in the English literature. This makes our case all the more interesting.

Recently, Economopoulos et al. reported 37 patients with primary NHL involving multiple extranodal sites at presentation. The majority of these cases (n = 26) had gastric or intestinal involvement with or without other extranodal sites. Lung along with another extranodal site was relatively common in their series. The remaining multifocal cases were patients with head and neck, bone, and testicular NHL. In the series of Economopoulos et al. of multifocal extranodal NHL, DLBCL was the most frequent histological subtype, comprising 62% of cases, as in our case [3].

In conclusion, clinicians should consider lym-

phoma in a patient with acute renal failure and bilaterally enlarged kidneys in the differential diagnosis. Furthermore, in any case of primary extranodal NHL, the patient should be fully evaluated to look for other unusual sites. In this way a greater number of asymptomatic sites can be detected contributing to a better therapeutic result.

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Renal cell carcinoma with pulmonary metastasis misdiagnosed as other primary malignant tumor

Dear Editor,

Renal cell carcinoma (RCC) is the 6th leading cause of cancer-related deaths [1]. Distant metastasis of RCC after 20 years from nephrectomy had been reported [2]. Herein, we described 2 patients with metastatic RCC. They were misdiagnosed and treated as primary non small cell lung cancer (NSCLC) after 17 and 7 years from radical nephrectomy.

A 62-year-old male had undergone left nephrectomy for stage I RCC, clear cell type in 1991. In 2007 he presented with cough, fatigue and weight loss. Thoracic CT showed a nodule in the right lower lobe and bronchoscopic specimens were histologically diagnosed as non small cell lung cancer (NSCLC). Cisplatin and docetaxel combination chemotherapy for 3 cycles and sequential radiotherapy were given to the patient. Due to disease progression, second-line and then third-line chemotherapy were administered. He was admitted to our oncology department and because of progression, misdiagnosis was suspected and pathologic specimens were re-evaluated. Microscopically the tumor cells had abundant clear cytoplasm and ovoid hyperchromatic nuclei with prominent nucleoli. Immunohistochemically the cells were positive for vimentin, EMA, CD10 but not for CEA, thyroglobulin, chromogranin, synaptophysin, NSE, TTF-1, CK7. These findings were compatible with lung metastasis from RCC. With sunitinib therapy the patient improved clinically for 6 months.

The other case was a 60-year-old man who had undergone right nephrectomy for stage II RCC, clear cell type in 2001. He was given 5 cycles of 5-fluorouracil, calcium leucovorin and interferon as adjuvant therapy and was disease-free for 7 years. The patient presented with weight loss, cough and hemoptysis in 2008. Chest CT demonstrated bilateral multiple metastatic lesions. Bronchoscopic biopsy revealed epithelial malignant tumor infiltration and histological diagnosis was primary NSCLC. Although carboplatin and paclitaxel combination was given as first-line chemotherapy, progression was detected radiologically. In our department, pathologic specimens were re-evaluated and RCC of clear cell type was diagnosed. Immunohistochemically the cells were positive for vimentin, EMA and CD10. Thereafter, therapy changed to sunitinib. Clinical improvement was seen under sunitinib therapy for 6 months.

Radical nephrectomy is standard treatment for RCC, however over 20% of patients relapse after radical nephrectomy. Relapses occur in 7% of T1 stage patients, in 16-26% of T2 and in 33-43% of T3 stage.

Eighty-five percent of the relapses occur within 3 years [1]. RCC metastasizes to the lung, liver, brain, bone and pancreas [3]. Clear cell type RCC is more likely to metastasize to the lung (53%) compared with papillary (33%) and chromophobe type (33%) [3]. Both of our cases had clear cell type RCC and metastasized to the lung. In the literature, RCC was shown to metastasize to the lung long after nephrectomy. There were 5 cases reports with an interval of more than 20 years [2]. Pfannschmidt et al. [4] concluded that longer interval between nephrectomy and lung metastasis was a better prognostic factor for the subsequent disease course. In our cases, pulmonary metastases were diagnosed 17 years and 7 years after nephrectomy, and were misdiagnosed and treated as NSCLC up to progression. After defining the correct diagnosis both patients received sunitinib. Although resection of pulmonary lesion(s) is suggested as treatment of choice [2], metastasectomy was not attempted in our cases because they were considered as primary advanced lung cancer.

When lung lesions are detected in patients with past history of RCC, even though long after nephrectomy, RCC should also be considered and the diagnosis should be confirmed histopathologically before treatment initiation.

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Cure of gemcitabine-induced systemic capillary leak syndrome without corticosteroids

Dear Editor,

Systemic capillary leak syndrome (SCLS), an episodic capillary hyper-permeability condition with intravascular fluid/ protein shift to interstitial space, is either idiopathic or secondary to underlying conditions or drug administration and is characterized by varying degrees of dyspnoea, oedema, hypoxaemia, pulmonary infiltrates or multiple serosal effusions, potentially progressing to fatal acute respiratory distress syndrome (ARDS). Gemcitabine (GEM) and other agents rarely induce SCLS.

In the last 10 years we attended 104 patients treated with GEM-containing chemotherapy who received 808 GEM injections. Only 3 (3.12%) patients, all with pancreatic cancer (2 men aged 56 and 71 and one woman aged 86) treated with GEM developed SCLS. One of them was additionally treated with weekly s.c. G-CSF injection, 48 h prior to his last 4 GEM injections. The patients developed dyspnoea and hypoxaemia, each after the 9th, 13th and 15th GEM injection, corresponding to the 85th, 107th and 124th day of treatment, respectively. On their admission, chest X-ray and CT scan showed diffuse bilateral lung infiltrates and bilateral pleural effusions in two, and pleural effusions with clear lung parenchyma in one. All were initially treated with oxygen 35-50% face mask and nadroparin, fearing the development of multiple pulmonary emboli. In addition, one patient was given antibiotics for suspected chest infection, one was administered diuretics for suspected cardiogenic pulmonary oedema, and one received furosemide and prednisolone because of face swelling, abrupt weight gain and pleural/ pericardial effusions with clear lung parenchyma. In

none of them thromboembolic disease, lower respiratory tract infection or heart failure were proved. In two, those with diffuse pulmonary infiltrates, SCLS resolved without corticosteroids (CS). All were discharged within 10 days, with all clinical abnormalities being settled. GEM was considered as causatively related to SCLS, while G-CSF might contribute in one patient. GEM was discontinued in all patients, although it was clinically beneficial in two. After SCLS remission, two patients survived for 4 and 9 months, and one is alive for 5 months.

Acute idiopathic SCLS is treated with respiratory support and intravascular volume loss replacement [1].

Treatment of GEM-induced SCLS remains essentially empirical, commonly consisting of various degrees of respiratory support, along with CS and diuretics [2]. In fact, the majority of GEM-induced SCLS cases respond to CS, while fatal cases, resistant to CS, have been reported. Although controversial, early and late ARDS controlled clinical trials support the administration of low- to moderate-dose CS (<7 days) [3].

After the first episode of SCLS, GEM discontinuation is recommended [2]. This may be enough for the regression of the syndrome. A few cases have been cured without CS as this was observed in two of our patients.

Besides, G-CSF rarely induces SCLS when applied in repeated daily doses, different to one of our cases. This has been described both in healthy progenitor blood cell donors [4] and after high dose cytarabine-based chemotherapy [5], and regresses with CS within a week.

The rare GEM-induced SCLS restricts patients from a palliative and marginally affecting survival drug, of otherwise good toxicity profile. Although not always necessary, a short course of CS seems safe and effective in most GEM-induced SCLS cases, always accompanied with GEM withdrawal.

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Delayed reaction after adjuvant whole breast radiotherapy at the dose of 42.9 Gy in 13 fractions over 5 weeks: the need for rapid post irradiation clinical assessment and who are the patients at risk?

Dear Editor,

Hypofractionated radiotherapy (RT) has been shown to be equivalent to normofractionated breast RT for patients treated for early-stage breast cancer in terms of local control and early toxicity [1-3]. In our Departments we delivered whole breast irradiation at a dose of 42.9 Gy/13 fractions (F)/5 weeks to selected patients who presented with tumors that did not require a boost to the tumor bed or lymph node irradiation. In most cases the patients were older than 65 years. Eighty-one prospectively recorded patients, treated in our departments between February 2006 and September 2007 have been studied. Skin reactions were monitored weekly using the National Cancer Institute-Common Toxicity Criteria scoring system, version 3. All risk factors such as tobacco smoking, diabetes, obesity were also recorded. All 81 patients, with median age of 70 years, received whole breast RT 42.9 Gy/13 F without lymph node irradiation after breast-conserving surgery. There were no patients with concurrent chemo and/or hormonal therapy.

During RT, only 34 (42%) patients experienced

Table 1. Evolution of skin reactions

Skin reaction (Grade)	*Week 3 = during RT Patients, n*	*Week 5 = at the end of RT Patients, n*	*Urgent visit for grade I skin reaction*	*Urgent visit for grade II skin reaction*	*Total n (%)*
0	47	15	1	1	2 (13)
I	34	59	8	10	18 (27)
II	0	7	0	0	0 (0)
Total	81	81	9	11	20 (25)

grade 1 skin reactions and 47 (58%) were without. On the last day of the breast RT, 59 had grade 1 and 7 grade 2 skin reactions, while no reaction was seen in 15 patients. The early skin tolerance of this scheme was considered excellent. But 2 weeks after RT completion, 20 (25%) patients showed increased skin reaction, as follows: 11 grade 1 and 9 grade 2 reaction (Table 1). The median time interval to the appearance of these reactions was 14 days (range 4-43). No grade 3-4 reactions were observed.

The evolution of these delayed skin reactions is given in Table 1. All patients were seen by their radiation oncologist, the skin reactions were re-evaluated and proper treatment, according to our protocols, was given [4]. Eleven patients needed more than one clinical advice. After analysis of the first group of 81 patients, compulsory clinical advice was given to all patients 14-20 days after the end of RT. This delayed reaction has been already reported [5], but the purpose of this report is to evaluate the candidates of careful follow-up during RT.

We found (Table 1) that the patients at risk for delayed skin reactions were those with grade 0-1 reactions at the end of RT. These patients finished their RT course without any symptoms and the appearance of delayed skin reaction was a source of anxiety. Patients who were already treated for their grade 2 reactions did not ask for any additional consultations.

After this experience we changed our practice using the treatment regimen of 41.6 Gy/13 F/5 weeks used in START A study [2].

As far as we know, this is the first description in the literature trying to assess this delayed skin reaction after 42.9 Gy/13 F/5 weeks and to determine the patients who will need supplementary clinics. This prospective homogeneous group of patients showed that delayed skin reactions could appear in some cases with median latency period of 14 days. Therefore additional clinical evaluations are needed to detect and treat these reactions. More studies should confirm our results.

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