A young woman with oedema

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(Intern Emerg Med 2006; 1 (3): 209-215)

Presentation and history

Prof. Paola Romagnani, Dr. Calogero Cirami, Prof. Maurizio Salvadori: A 31-year-old woman came to our observation because of persisting oedema. Three years before, the patient underwent allogenic stem cell transplantation from her HLA identical brother because she suffered from an acute lymphoblastic leukaemia. The leukaemia was FAB L1 peroxidase negative and 60% of the cells in the bone marrow were CD34+, CD13+, CD33+, CD15+, CD4+, HLA-DR+ blasts. Conventional cytogenetic analysis was unsuccessful and Bcr/Abl detection by FISH was negative. After disease remission following one course of induction therapy, the patient completed one cycle of consolidation therapy with cytarabine and mitoxanthrone, although meanwhile she underwent an acute respiratory distress syndrome that required intensive treatment. Cyclosporine A and methotrexate were administered as prophylaxis for graft-versus-host disease (GVHD). The post-transplant period was uneventful. Periodic controls always yielded negative results. As could be expected, the above-mentioned treatments generated an ovarian failure, which manifested through a persisting amenorrhea. Thus, 2 years after allogenic stem cell transplantation, the patient started hormone replacement therapy (HRT) with estradiol valerate (2 mg) and medroxyprogesterone acetate (10 mg). After 2 weeks of HRT, she began to suffer from generalised oedema, mainly periorbital and pretibial, which were more evident in the morning and resulted in weight increase. HRT was stopped, which resulted in an improvement of oedema. After a few days, HRT was administered again, but a significant increase in the oedema occurred. Therefore, HRT was again stopped and treatment with diuretics was introduced. The severity of the oedema worsened, and its preferential localisation to periorbital areas suggested a possible renal origin, even though the laboratory tests performed immediately before beginning the HRT had shown normal serum albumin levels, normal renal function (creatinine 1 mg/dl or 88 µmol/l), and the absence of either proteinuria or alterations of urine sediment.

Differential diagnosis of oedema

Prof. Romagnani, Dr. Giuseppe Stefano Netti: The first clinical question we needed to solve was to define the cause of the generalised oedema, which represented the initial symptom in this patient. Oedema is defined as a palpable swelling produced by expansion of the interstitial fluid volume. Oedema can be localised (mostly due to allergic reactions, venous or lymphatic diseases), or generalised, as it was in this patient. For the occurrence of a generalised oedema to occur, two mechanisms should be operating: (a) an alteration in capillary haemodynamics that favours the movement of fluid from the vascular space into the interstitium, related to increased capillary hydrostatic pressure, decreased capillary oncotic pressure, or increased capillary permeability; (b) the retention by the kidneys of dietary or intravenously administered sodium and water, which can be either a primary event, as in renal failure, or a secondary event resulting from a primary reduction in cardiac output (as in heart failure) or systemic vascular resistance (as in cirrhosis).

The history is obviously important, and the physical examination can also aid in establishing the proper diagnosis. The oedema following left ventricular dysfunction is usually peripheral, and may be associated with pulmonary congestion, or in more severe cases, with pulmonary oedema. In these patients, the peripheral oedema is a minor sign, whereas the pulmonary oedema is a life-threatening event. It is associated with shortness of breath, orthopnoea and chest pain, which may be the prominent symptom if pulmonary oedema is due to an acute myocardial infarction. By contrast, patients with right-sided heart failure

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have peripheral oedema, and in more severe cases, anasarca with ascites and oedema of the abdominal wall. Shortness of breath is commonly present, and may be due to underlying pulmonary disease or coexistent left ventricular failure. Cirrhotic patients can develop ascites and then oedema of the lower extremities because of an increase in venous pressure below the diseased liver, as well as a decreased oncotic pressure. A primary hepatic disease has to be suspected if there are other signs of portal hypertension, such as distended abdominal wall veins, splenomegaly or spider angiomata.

Patients with renal disorders can develop generalised oedema, mostly related to nephrotic or nephritic syndromes. Patients with nephrotic syndrome typically exhibit periorbital and peripheral oedema, and sometimes, ascites. Two factors contribute to retain fluids in this condition: primary sodium retention due to the underlying renal disease, and often, less importantly, also due to a diminished transcapillary oncotic pressure gradient, mostly associated with very severe hypoalbuminaemia[1].

The diagnosis of a nephrotic syndrome is confirmed by documenting the presence of oedema in association with both heavy proteinuria (usually > 3-3.5 g/day) and hypoalbuminaemia. Lipiduria and hyperlipidaemia are also seen in many patients. Nephritic syndrome mainly leads to a decrease of glomerular filtration rate followed by renal sodium retention and increased capillary hydrostatic pressure, with subsequent combined pulmonary and peripheral oedema. The physical findings are similar to those found in patients with heart failure, but an abnormal urinalysis (particularly if there are signs of active renal disease, such as red cell casts) and elevations in the blood urea nitrogen and plasma creatinine concentration usually enable the physician to distinguish an underlying renal disease from heart failure. HRT may also have a role in inducing oedema in women through two possible mechanisms: (a) the activation of the bradykinin system in patients with hereditary angio-oedema and C1 esterase inhibitor deficiency[2]; (b) an increased renal sodium retention via aldosterone-like activity[3]. However, generalised HRT-related oedema is usually mild, and, more importantly, it undergoes spontaneous resolution after stopping treatment.

Our patient did not have a history of coronary disease, hypertension, alcohol abuse or treatment with drugs that can cause cardiac or hepatic disease. Moreover, after definitive suspension of HRT, the generalised oedema did not improve. Head, neck and chest examinations were normal. Furthermore, she did not have hepatomegaly or splenomegaly, as well as no signs of ascites or portal hypertension. The main pretibial and periorbital localization of oedema suggested a renal involvement, which made it mandatory to obtain a new investigation of the renal function and of urine sediment.

Further investigations

Prof. Salvadori, Dr. Cirami: After HRT suspension, the laboratory analyses revealed an increased serum creatinine (1.7 mg/dl or 150 μmol/l) and the appearance of proteinuria (4+ on dip strips/stick) and microhaematuria (Hb++, red blood cells 25-50/hpf) at the urinalysis. Since a worsening of the generalised oedema continued to occur, the patient was admitted to our hospital.

On physical examination, she showed a weight of 54 kg for 1.65 m height, temperature was 36.5°C, blood pressure was 150/90 mmHg; heart rate 90 bpm. No abnormalities were revealed on the abdominal, neurologic and musculoskeletal examinations. The white cell count was 5190 $\times$ 10^3 cells/mm^3, with a balanced differential white cell count, the haematocrit was 35%, the platelet count was 290 $\times$ 10^3 cells/mm^3; the international normalised ratio (INR) was 0.9, the activated partial thromboplastin time was 28 s and fibrinogen was 480 mg/dl. All viral markers were negative. Anti-streptolysin antibody titre was normal. The serum levels of electrolytes, aminotransferases and total bilirubin were normal. The total protein level was 4.1 g/dl, the albumin level was 1190 g/dl, α_2-globulins were increased and γ-globulins reduced. The serum level of IgG was 389 mg/dl, IgA, IgM and complement levels were normal, total cholesterol levels were 390 mg/dl. The serum creatinine level was 1.8 mg/dl (159 μmol/l), and blood urea nitrogen level was 59 mg/dl. The urinalysis confirmed the existence of proteinuria (++++) and microhaematuria (Hb++). The daily proteinuria was equal to 12 g.

Preliminary diagnosis

Prof. Salvadori, Dr. Cirami: The clinical presentation was consistent with a preliminary diagnosis of acute renal failure due to nephrotic syndrome in a patient with a history of acute leukaemia treated with allogenic stem cell transplantation.

Discussion of preliminary diagnosis

Prof. Romagnani: Renal disease as a consequence of bone marrow transplantation (BMT) has considerably increased during the last few years. It may develop as both acute and chronic renal failure. Both the ever-growing number of BMT patients, and the increasing short-term and long-term survival of patients undergoing BMT probably account for this phenomenon. Currently, 5-15% of all patients undergoing BMT may develop acute renal failure and 5-20% of them will

develop chronic renal failure[4]. The typical acute renal failure that is seen in the first 30 days after BMT occurs more often after allogeneic than after autologous BMT, and it has been associated with sepsis, hypotension, use of nephrotoxic antibiotics, and concurrent liver disease[4]. Another cause of acute as well as chronic renal failure may also be the nephrotoxicity of the calcineurin inhibitors cyclosporine A or tacrolimus, which are used in the first few months after allogenic BMT to prevent GVHD. Indeed, 6 months after BMT, surviving patients have a mean serum creatinine level almost 2.5 times higher than baseline values[5]. Treatment of these toxicities frequently requires suspension of cyclosporine A administration, which in turn may predispose to the development of GVHD and its numerous and serious sequelae[5]. Of note, chronic renal failure after BMT was recognised over 10 years ago as a sequela of the total body irradiation used for conditioning and its incidence has increased in the last few years[4]. Radiation nephropathy usually occurs 8-12 months after BMT, and is clinically characterised by hyperazotaemia, hypertension, and severe anaemia. If untreated, this nephropathy leads to end-stage renal failure requiring dialysis or kidney transplantation. Structural features include mesangiolysis, sclerosis, tubular atrophy, and tubulointerstitial scarring[4,5].

However, the clinical picture in our patient was different: indeed, it was renal failure associated with a sudden onset of a nephrotic syndrome. In a young non-diabetic adult, the nephrotic syndrome is mainly due to glomerulonephritis (GN), either primary or secondary to collagen vascular diseases, infections, malignancies, toxic agents or medications. The most common form of GN causing nephrotic syndrome is membranous GN, followed by focal segmental glomerulosclerosis, and minimal change disease (MCD).

Although nephrotic proteinuria has been described as an atypical form of extensive chronic GVHD, several cases have been reported. Histopathologically, most cases show membranous nephropathy[6-20], whereas some others exhibit MCD[16,21-26].

Analysis of the renal biopsy and bone marrow aspirate

Prof. Salvadori, Dr. Elena Lazzeri: To establish which was the glomerulopathy underlying the nephrotic syndrome in our patient, a renal biopsy was performed. Light microscopy showed a massive infiltrate of mononuclear cells (MNCs) in the interstitium (Fig. 1A) and in the periglomerular areas. However, glomeruli were normal, without crescents, areas of segmental glomerulosclerosis (thus excluding focal segmental glomerulosclerosis) or membrane thickening (that may suggest a membranous GN), as also confirmed by PAS reaction (Fig. 1B). Immunofluorescence did not reveal the presence of immune deposits (IgM, IgG, IgA, C3) or fibrinogen. Electron microscopy demonstrated effacement of podocytes foot processes and confirmed the absence of dense deposits. Glomerular analysis was consistent with MCD, the most relevant finding being the diffuse infiltration of MNCs (Fig. 1A). To exclude the possibility of a leukaemia relapse at a medullary level, a bone marrow aspirate was performed, which gave negative results. Meanwhile, the patient's proteinuria reached 28 g/day and serum creatinine rapidly increased (3.7 mg/dl or 326 μmol/l).

Discussion for differential diagnosis

Prof. Romagnani, Dr. Lazzeri, Dr. Netti: Based on the biopsy picture, chronic GVHD could be hypothesised but, given the strong association of MCD with lymphoproliferative disorders[27,28] we were mainly worried about a re-

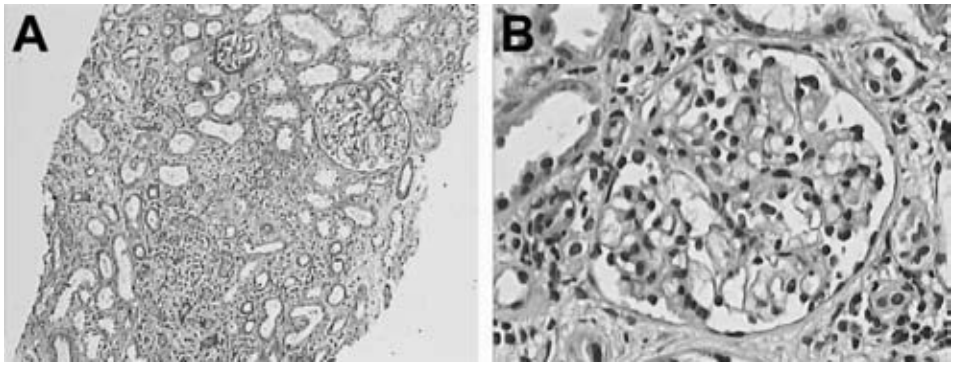

Figure 1. Light microscopy assessment of the renal biopsy. *A:* renal biopsy specimen showing diffuse mononuclear cell infiltrate and normal glomerular structures (periodic acid-Schiff reaction; original magnification ×100). *B:* high power magnification of a glomerular structure showing normal morphology and periglomerular infiltrating cells (haematoxylin-eosin reaction; magnification ×400).

lapse of leukaemia. Indeed, the appearance of an isolated MNC infiltrate in a solid organ is a frequent occurrence in a bone marrow-transplanted patient, and an important possible cause is a relapse of the leukaemia, which can present as either haematopoietic (involving bone marrow and peripheral blood), or extramedullary (involving other sites)[29]. Extramedullary relapses of acute leukaemia after BMT are as frequent as 50% of all relapses[30]. About 40% of extramedullary relapses occur without concomitant haematopoietic relapse[31]. The central nervous system and testes are the predominant sites of isolated extramedullary disease. However, relapses can involve other isolated sites, including liver and uterus, pancreas and retroperitoneum, pericardium and mediastinum, breast, lung, pleura, bone and soft tissue, intestine, nasopharynx, sinus, skin, ovary, heart, eye and kidney[29-33].

During the past few years, so-called autoimmune privilege has been postulated as a cause for frequent relapse sites, such as the central nervous system, the testicles and the anterior chamber of the eye. Impaired accessibility of these organs by cytotoxic T cells with a reduced graft-versus-leukaemia effect after allo-haematopoietic stem cell transplantation is based on a number of different molecular and cellular mechanisms. Similar mechanisms have been shown to also be effective in the tubulointerstitial space of the kidney, rendering the kidney a potentially immune privileged site, and thus making it a possible site of extramedullary relapses[30-33]. Generally, treatment of extramedullary relapses consists of local radiotherapy or chemotherapy[29-33], but successful outcome is closely related to prompt initiation of treatment. GVHD is another possible frequent cause of an isolated MNC infiltrate in a solid organ of a bone marrow-transplanted patient. Chronic GVHD generally develops at least 2-3 months after BMT, presents as a systemic autoimmune disorder, and occurs in about 50% of long-term survivors. Symptoms and signs involve skin, liver, mouth, eyes, gastrointestinal or upper respiratory system. While liver and skin involvement are very frequent, selective renal involvement is rare. When other characteristic clinical signs are lacking, the isolated presence of a mononuclear infiltrate in a solid organ can make it very difficult to distinguish between GVHD and an extramedullary relapse of leukaemia by means of currently available diagnostic assays.

Differential diagnosis

Prof. Romagnani, Dr. Lazzeri: The patient had a severe nephrotic syndrome due to a MCD, but the most significant finding in the renal biopsy specimen was the massive inflammatory infiltrate. During admission to our service, the patient developed a rapidly progressive worsening renal failure, and an appropriate therapy was urgently required to save the life of the patient as well as her kidneys. Nevertheless, it was imperative to clarify the diagnosis between a relapse of the primary lymphoproliferative disorder and an isolated renal involvement due to an atypical form of chronic GVHD.

Molecular analysis of infiltrating mononuclear cells

Prof. Romagnani, Dr. Lazzeri, Dr. Benedetta Mazzinghi: Renal biopsy immunohistochemical staining demonstrated that infiltrating MNCs were mostly CD8+ T lymphocytes, whereas they did not show any reactivity with an anti-CD34 antibody, suggesting that these cells did not belong to the original leukaemic population. Subsequently, to provide direct evidence, MNCs were recovered using laser capture microdissection and a microextraction of DNA was performed (Figs. 2A and 2B). Identical surface samples obtained from the same renal biopsy in an adjacent area where MNCs were absent, as well as from another biopsy obtained from a male kidney, were used as controls (Figs. 2A and 2B). It was reasonable to hypothesise indeed that in our patient after BMT from her HLA identical brother, a chronic GVHD should be provoked from cells bearing an Y chromosome, whereas cells resulting from an extramedullary relapse of leukaemia should exhibit an

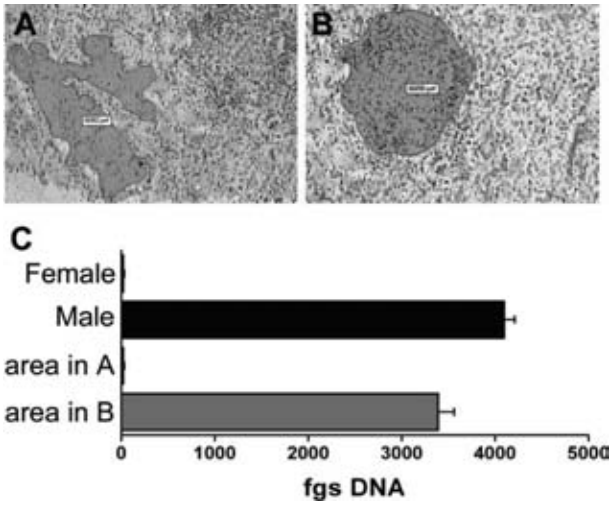

Figure 2. Differential diagnosis of nephrotic syndrome using molecular tools. *A:* an area (66 902 μm^2) was recovered from the renal biopsy specimen by using laser capture microdissection on a zone free of infiltrating mononuclear cells (original magnification $\times$250). *B:* infiltrating mononuclear cells were recovered from an area of 66 890 μm^2 (original magnification $\times$250). *C:* quantitative assessment of DNA levels shows that infiltrating cells (area in B), but not resident renal cells (area in A), in our patient show levels of a Y chromosome-specific gene similar to those observed in a male subject.

XX cariotype. Taq-Man quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) performed on DNA extracted from kidney biopsy specimens demonstrated that infiltrating MNCs displayed a number of copies of the SRY gene (a transcription factor selectively localised on the Y chromosome) comparable to that observed in the kidney of a male subject (Fig. 2C, area in B). By contrast, no copies of SRY DNA were found in the adjacent area from the kidney biopsy of the patient, where no infiltrating MNCs were detectable (Fig. 2C, area in A).

Diagnosis

Prof. Romagnani: These findings unequivocally demonstrated that infiltrating MNCs in the kidney of the patient were T cells derived from the transplant donor, definitely excluding a relapse of leukaemia, and supporting the diagnosis of MCD in the context of a chronic GVHD.

Discussion of diagnosis

Prof. Romagnani: A sudden onset of nephrotic syndrome after BMT is considered to be a rare occurrence. However, two recent studies report a high occurrence of nephrotic syndrome in bone marrow-transplanted patients. The cumulative incidence of nephrotic syndrome is 8% in one study[34], and 6.1% in another study[35]. Interestingly, patients grafted as was ours with peripheral blood stem cells, have a higher probability of developing nephrotic syndrome than those grafted with bone marrow: 24% and 3%, respectively[34]. The nephrotic syndrome is usually associated with clinical signs and symptoms of chronic GVHD[34,35]. The pathological diagnosis is usually that of membranous GN, while MCD has rarely been reported.

MCD is a disorder caused by injuries to the glomerular epithelial foot processes due to T-cell-released cytokines. This, in turn, leads to a decreased synthesis of polyanions, which constitute the normal charge barrier to the filtration of macromolecules, thus allowing albumin leakage to occur[36]. Almost all cases are idiopathic, but approximately 20% of them have an identifiable cause, such as drugs (non-steroidal anti-inflammatory drugs, rifampin, interferon, penicillin, trimethadione), toxic agents (mercury, lithium, bee stings), infections (mononucleosis, HIV, immunization) or tumours (most commonly Hodgkin's lymphoma and lymphoblastic leukaemia; rarely carcinomas)[37].

Of note, in our patient, the nephrotic syndrome began immediately after initiation of HRT, required for treatment of an irreversible gonadal failure. Although several experimental data suggest that the development and activity of GN related to chronic GVHD may be influenced by sex hormones, a recent study performed on 39 bone marrow-transplanted women, has pointed out that HRT does not influence the activity of chronic GVHD and can be performed safely[38]. In our patient, given the strict temporal relationship between HRT and GVHD-related nephrotic syndrome, a correlation between the two events cannot be excluded.

Another possibility to explain the occurrence of the nephrotic syndrome and renal failure could be its occurrence during the course of a lymphoproliferative disorder[27,28]. A GN may indeed precede, coexist, or follow the diagnosis of lymphatic malignancy by several years. At autopsy up to 90% cases (range 63-90%) have kidney infiltration[39-41]. Thus, given the strong association of MCD with lymphoproliferative disorders, and the high frequency of extramedullary relapses after BMT[31], a relapse of leukaemia was highly probable. A nephrotic syndrome in an adult subject is an absolute indication for renal biopsy, which usually settles the question. However, in a patient with a BMT-treated leukaemia, involvement of a single organ by a MNC infiltrate frequently occurs, and it always raises the problem of a differential diagnosis between an extramedullary relapse of leukaemia or a chronic GVHD. Although the clinical context usually helps to reach the right diagnosis, in some cases the absence of other symptoms makes it impossible to differentiate between the diagnoses on the basis of clinical evidence and currently available diagnostic assays. In these cases, the patient is usually treated empirically with immunosuppressive agents, with high risk due to the wrong treatment bearing severe side effects, and with a dangerous delay in the initiation of the correct therapy. To avoid any of these problems in our patient, we used laser capture microdissection combined with Taq-Man quantitative RT-PCR as a rapid, highly specific tool to discriminate between the two possibilities. This novel diagnostic approach unequivocally excluded the relapse of leukaemia, and made certain the diagnosis of chronic GVHD.

Management and clinical follow-up

Prof. Romagnani, Dr. Cirami, Prof. Salvadori: Following the diagnosis of chronic GVHD, the patient was treated with oral prednisone with a daily dosage of 1 mg/kg of body weight for 12 weeks, which was then slowly tapered in the attempt to reduce the likelihood of relapse. After 3 months of treatment, the proteinuria disappeared and the renal function was completely restored, with serum creatinine levels equal to 0.9 mg/dl (80 µmol/l). Two years after steroid withdrawal, the patient is still in good health.

Acknowledgements

The experiments reported in this paper were supported by funds from the Italian Association for Cancer Research (AIRC), from the University Hospital of Florence, from the Italian Ministry of Health and from the Italian Ministry of University and Scientific Research (MIUR).

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