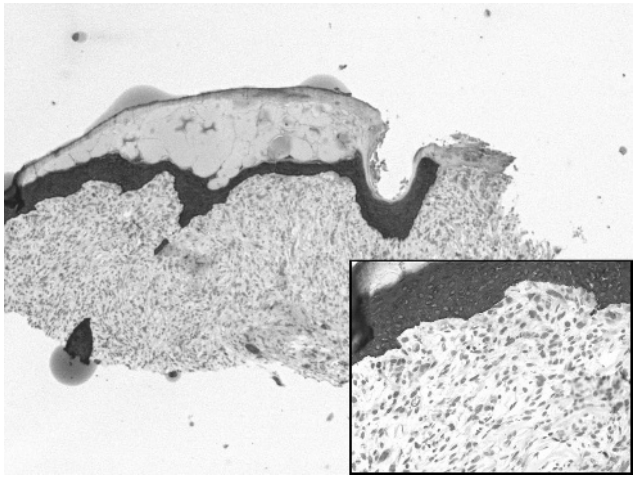

Figure 2 Atypical fibroxanthoma: case 2, cytokeratin stain. Note the faint dermal cytokeratin positivity.

antigens in their course of differentiation. Phagocytosis of CKs from other cells and adnexa is also a possibility. Conversely, these neoplasms may actually be de-differentiated squamous-cell carcinomas that have lost their epithelial antigens.

It is important to realise the inherent uncertainty in the diagnosis of poorly differentiated cutaneous malignant spindle-cell neoplasms. The most reliable way to distinguish these neoplasms is immunohistochemistry; however, dermatopathologists must keep in mind the capabilities and limitations of immunohistochemistry. Aberrant CK expression can occur in AFX. It is important not to overinterpret this aberrant staining, which might lead to an erroneous diagnosis.

Cheryl Bansal
Department of Dermatology, Drexel University College of Medicine, Philadelphia, Pennslyvania, USA

Prasanna Sinkre, David Stewart, Clay J Cockerell
Department of Dermatology, Division of Dermatopathology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence to: C Bansal, Drexel University College of Medicine, 2967 Schoolhouse Lane, Apt C-602A, Philadelphia, PA 19144, USA; cb59@drexel.edu

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Pure red cell aplasia associated with type I autoimmune polyglandular syndrome—successful response to treatment with mycophenolate mofetil: case report and review of literature

Pure red cell aplasia (PRCA) is a rare haematological syndrome characterised by anaemia, reticulocytopenia and severe erythroid hypoplasia without alteration in megakaryocytic and myeloid maturation. Immune system irregularity can be mediated by the presence of autoantibodies against erythroid cells or against erythropoietin (Epo), or by hyperactivity of large granular lymphocytes with enhanced T cell or natural killer cell cytotoxicity.[1–3] The association between PRCA and other autoimmune diseases such as autoimmune polyglandular syndrome (APS) I is rare.[4]

The second autoimmune disease, named APS I or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare hereditary autosomal recessive disorder. It is characterised by the presence of chronic mucocutaneous candidiasis, multiple endocrinopathies (hypoparathyroidism, adrenocortical failure, hypergonadotropic hypogonadism, type I diabetes mellitus and panhypopituitarism), and various ectodermal manifestations (enamel dysplasia, nail dystrophy, alopecia, vitiligo and keratopathy).[5 6] Clinically, APECED can be confirmed by appearances of at least two of the three features: candidiasis, hypoparathyroidism and adrenocortical failure.[5–7] This is the first multiple autoimmune disorder shown to be caused by mutations of a single gene—the autoimmune regulator gene (AIRE).[8] This gene was mapped at 22q22.3 and consisted of 14 exons.[8] It is expressed in immune-related organs, such as thymus, lymph nodes and fetal liver, indicating that it has a pivotal role in the immune function. Its main role is to act as a transcriptional factor. Over 40 different mutations of the AIRE gene have been identified (point mutations, insertions and deletions).[8 9]

Case report

A 33-year-old woman was admitted to the Institute of Haematology, Belgrade, Serbia, in April 2001 for blood transfusion for the treatment of anaemia. The diagnosis of idiopathic hypoparathyroidism was made at age 7 years. At age 14 years, she developed idiopathic adrenal insufficiency and 2 years later, she developed mucocutaneous candidiasis. Since early infancy, she had had alopecia universalis. The patient had dysfunctional thyroid nodule, with positive anti-tireoglobuline and anti-microsomal antibodies. She had had euthyroid and amenorrhoea for the last 3 years. Her younger sister developed chronic mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency, pernicious anaemia and lichen ruber planus. The DNA samples from the patient and her sister were additionally tested for a nonsense mutation in exon 6 (R257X) of the AIRE1 gene. PCR analysis and direct sequencing showed that both sisters were homozygotic for the R257X mutation. This change in arginine resulted in a truncated gene product. Physical examination revealed marked pallor, alopecia and oral candidiasis without lymphadenopathy or hepatosplenomegaly. MRI excluded the presence of thymoma. Laboratory findings revealed a haemoglobin level 60 g/l, red blood cells 1.4×10^{12}/l, haematocrit 13.7%, mean corpuscular volume 115 fl, reticulocytes 0.0%, platelets 395×10^{9}/l and white blood cells (WBCs) 11.7×10^{9}/l (segmented neutrophils 15% and lymphocytes 85%). Morphologically, lymphocyte populations dominantly consisted of small lymphocytes (43%), partly small T lymphocyte with irregular nucleus (22%) and larger activated lymphocytes (20%). The Coombs test was negative. The increased haemolysis and paroxysmal nocturnal haemoglobinuria were ruled out. The serum Epo level was markedly increased (47.3 mIU/ml) in comparison to reference values (9.9 (2.9) mIU/ml; range 7.0–12.8 mIU/ml). Further studies revealed normal values for serum ferritin, transferin, vitamin B_{12} and folic acid. Tests for antibodies against human parvovirus B19, cytomegalovirus, HIV, hepatitis B, C, and Epstein–Barr virus were negative. Antinuclear antibody, rheumatoid factor and anti-DNA antibody were not detectable. Bone marrow aspirate showed hypercellularity (>III), a lack of erythroid precursors (2% of bone marrow nucleated cells), normal granulocyte precursors (75%) and megakaryocytes, 16% of lymphocytes, 4% of plasmocytes and 3% of monocytes. Bone marrow biopsy revealed slight hypercellularity with normal maturation of the myeloid lineage and megakaryocytes, but <1% of the cells were erythroid precursors (including proerythroblasts). There was no increase in the blast count. The karyotype was normal. Immunophenotyping (Flow cytometry, Becton Dickinson, San Jose, USA) performed on peripheral blood cells showed that 91% (8.21×10^{9}/l) of all cells were mature T lymphocytes (CD2, CD3, CD5, CD7, CD4 or CD8, T cell receptor (TCR)α/β or TCRγ/δ)+. T cell subsets expressed 62.98% (5.15×10^{9}/l) of the TCR α/β+ T cells and 28.69% (3.06×10^{9}/l) of TCRγ/δ+ cells. A small subset, 9% (0.89×10^{9}/l), of mature phenotype B lymphocytes (CD19, CD20, CD24, SIg, κ or

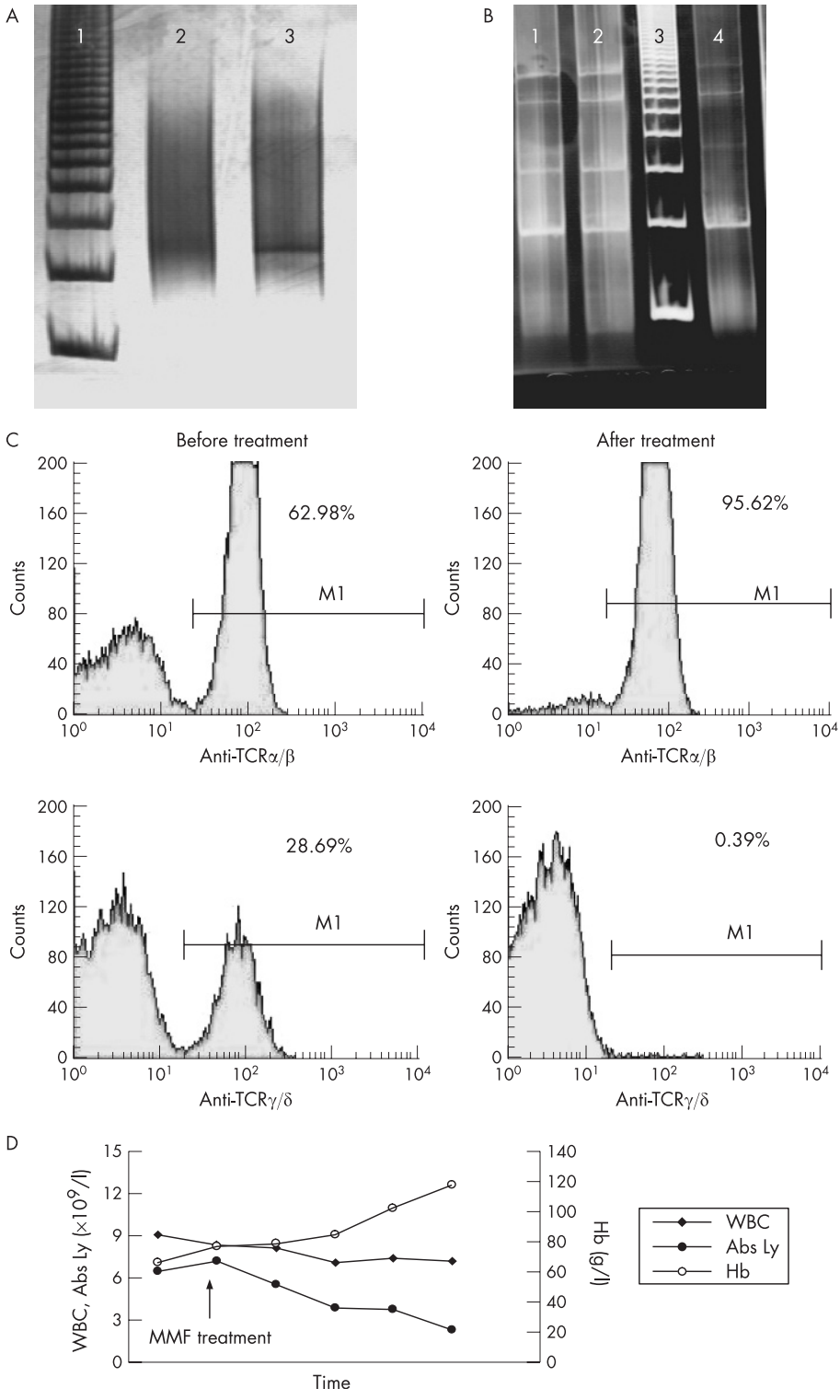

Figure 1 (A) PCR analysis of T cell receptor (TCR) γ rearrangement: line 1, marker; line 2, healthy patient; and line 3, patient sample (monoclonal pattern between 450 and 500 bp). (B) PCR analysis of IgH rearrangement. Lines 1 and 2 are healthy controls, line 3 is marker and line 4 is patient (smear). (C) Flow cytometry data for α–β and γ–δ T cell subsets before and after treatment. (D) Clinical course of disease estimated by the determination of total white blood cell (WBC) count, absolute lymphocyte count (Abs Ly) and haemoglobin (Hb) concentration. MMF, mycophenolate-mofetil.

λ)+ was found. There was an inverse relationship between subsets of T lymphocytes (CD4/CD8 = 0.6) with complete absence of natural killer cells (CD16 = 0%). Rearrangements of TCR α/β or TCR γ/δ were examined by the PCR technique. PCR conditions used for the TCRδ region were as follows: denaturation step at 94℃ for 10 min, followed by 35 cycles of denaturation at 94℃ for 45 s, annealing at 65℃ for 30 s and extension at 72℃ for 1 min. Nested PCR (two rounds) was used for TCRγ rearrangement analysis. Primers TCRγ1 and TCRγ2 were used for the first PCR round, and primers TCRγ3 and TCRγ4 for the second PCR round (table 1). PCR conditions used for TCRγ region were as follows: denaturation step at 94℃ for 10 min, followed by 30 cycles of denaturation at 94℃ for 10 s, annealing at 58℃ for 20 s and extension at 72℃ for 1 min. PCR analysis was followed by electrophoresis on 8% polyacrylamide gel. We found rearranged TCRγ and TCRδ with PCR products (between 450 and 500 bp, respectively), but without IgH rearrangement (fig 1A,B). The

bone marrow cell culture performed in standard semisolid methylcellulose medium showed normal numbers of erythroid and granulocytic progenitors. We also found 116 burst-forming unit-erythroid (BFU-E) and 70 colony-forming unit-granulocyte macrophage (CFU-GM) colonies growing spontaneously in comparison to reference values, which were 40–180 for BFU-E and 38–120 for CFU-GM, respectively. The number of Epo-stimulated colonies (Epo-CFU-E) was 163 and 181 with 0.5 and 1.0 U of Epo, respectively. These findings indicated that the level of inhibition of Epo was between CFU-E and proerythroblast. Different dilutions of the patient's serum showed significant inhibition of growth Epo-stimulated BFU-E colonies of healthy donors, in a dose-dependent manner from 13.58% to 100%. Cocultures of separated T lymphocytes from the patient with allogenic bone marrow cells from healthy donors after Epo stimulation showed inhibition of BFU-E (at 56% from reference values). These in vitro tests showed that both mechanisms (cellular and humoral) were involved in the inhibition of growth of Epo-stimulated BFU-E colonies.

On account of the patient's severe anaemia and frequent transfusions, treatment was started with prednisolone (40 mg/day) and ciclosporin A (CyA; 5 mg/kg/day) after obtaining informed consent of the patient. Anaemia was partially improved by this treatment, but was followed by a decrease in T lymphocyte count and severe renal dysfunction (acute nephrotoxicity). Therefore, we reduced CyA to 100 mg/d after 3 weeks of initial treatment. During the next 4 months, the patient received treatment along with continuing substitution for APECED (hydrocortisone, Vitamin αD3, fluconasole). Unfortunately, her Hb decreased maximally to 65 g/l. Therefore, we decided to start treatment with mycophenolate-mofetil (MMF; CellCept, 2 g/day). After a period of 4 months, we observed complete haematological recovery with almost normal value of Hb (119 g/l) and lymphocytes 2.3×10^9/l (23% of WBC), without nephrotoxicity (fig 1D). After 3 years of immunosuppressive treatment, the patient had normal blood cell count and progression of other autoimmune phenomena—primary ovary insufficiency and exocrine pancreatic insufficiency. Repeated flow cytometric analysis showed prominently (significantly) a decreased number of γ/δ TCR+ lymphocytes. PCR analysis showed that these cells had monoclonality for TCRγ/δ. Additional double-stained cells analysed by flow cytometry after treatment showed a significant decrease (1.25%) in the CD4+CD25+ T regulatory cells (T reg). The other cell subsets were 76.10% for CD38+CD3+ cells and 70.68% for human leucocyte antigen (HLA)-DR+CD3+ cells. After treatment with MMF, we analysed the sensitivity of peripheral blood lymphocytes (PBLs) to apoptosis using annexin-V and propidium iodide, flow cytometry as well as TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labelling) assay (Roche, In Situ Cell Death Detection Kit, AP, Roche, Basel, Switzerland). Results showed significantly higher rates of apoptosis and late necrosis of patient's lymphocytes cultured for 24 h in the presence of different sera (55.74%, 55.07% and 47.76% for autologous, heterologous and fetal calf serum, respectively) in comparison with healthy controls (23.82%, 23.04% and 29.05%, respectively; $p<0.05$, Mann–Whitney U test). We obtained identical results by two different assays showing that total number of PBLs of patients have a high rate of apoptosis and necrosis (87.5%). To address the question about the high rate of apoptosis after treatment, we found that PBLs expressed a high level of FAS (CD95) antigen (60%) detected by immunocytochemical analysis using monoclonal antibody anti-CD95 (Dako, Glostrup, Denmark).

Table 1 Primer sequences for PCR analyses

TCRδ1: 5′-GAGTCATGTCAGCCATGAG-3′
TCRδ2: 5′-AGGGAAATGGCACTTTTGCC-3′
TCRγ1: 5′-CTGTGACAACAAGTGTTGTTCCAC-3′
TCRγ2: 5′-GTGCTTCTAGCTTTCCTGTCTC-3′
TCRγ3: 5′-GAGTACGCTGCCTACAGAGAGG-3′
TCRγ4: 5′-CCACTGCCAAAGAGTTTCTT-3′

TCR, T cell receptor.
Primer TCRδ1 amplifies from the V2 gene, TCRδ2 from the D3 sequences, TCRγ1 from J1/J2, TCRγ2 from V1–V8, TCRγ3 from V1–V8 and TCRγ4 from J1/J2.

Discussion

Acquired PRCA is mostly considered to be of an autoimmune aetiology because of antibody-mediated or T cell-mediated inhibition of erythropoiesis.[4] Involvement of the immune system in the pathogenesis of PRCA has been documented previously. Here, we reported that T cells mediated some immune phenomenon in PRCA associated with APECED based on the predominant expression of T cell subsets (23.60%) with γδ+ TCR rearrangements. Further analyses showed that these lymphocytes had clonal molecular abnormality confirmed by DNA analysis. The TCRαβ+ lymphocyte subset was also significantly expanded (60.98%) in peripheral blood but without monoclonality. Some reports indicated that most cytotoxic γ/δ T cells express killer-cell inhibitory receptors, suggesting that they survey the body for missing self HLA-class I alleles.[10] It might be that γ/δ T cells can destroy erythroid progenitors in vivo by downregulation of HLA class I antigens in the erythroid lineage.

The clinical course in this patient also showed a strong correlation between the decreased number of total lymphocyte count and recovery from PRCA. This observation suggested that the γδ TCR+ cell subset that is not MHC restricted can be functional in vivo and be involved in the pathogenesis of PRCA.[4] They can exert a suppressive effect on erythropoiesis mainly through a soluble product rather than by direct cell-to-cell interaction. In our patient with PRCA, selective suppression of erythropoiesis by both T cells and cell supernatants has been demonstrated.

We also showed that after oral immunosuppressive treatment with the new drug, MMF, depletion of T cells was achieved by induction of apoptosis. MMF is a new immunosuppressive drug, primarily used for renal transplantation,[11] which inhibits de novo purine synthesis. MMF as a prodrug of mycophenolic acid (MPA) is an inhibitor of inositol monophosphate dehydrogenase. MMF and MPA have a more potent cytostatic effect on T and B lymphocytes than on other cell subsets. We, like others, showed that their effects can be mediated by the induction of apoptosis in activated T lymphocytes, and by elimination of reactive cell clones.[12 13] MPA can suppress glycosylation and decrease expression of adhesion molecules by depleting guanosine nucleotides; thus, MPA decreases the activity of tetrahydrobiopterin, a cofactor for the inducible form of nitric oxide synthase, and suppresses primary, but not secondary, antibody responses. MMF does not inhibit early TCR-mediated activation events, such as expression of CD25 and synthesis of interleukin2.[13]

Also, MMF can induce apoptosis of activated T lymphocytes, which may eliminate clones of cells responding to antigenic stimulation.[13] In patients with autoimmune lymphoproliferative syndrome, apoptosis of T lymphocytes is achieved through activation of mutating FAS (CD95) receptor.[14]

The rate of apoptosis induced by MMF in our investigation is similar to other data showing that therapeutic levels of MMF, ranging in concentrations from 3 to 7 μg/ml, increased apoptosis rates from 56% to 67%.[15] In our patients with PRCA and APSI, we found a significantly decreased T reg lymphocyte population (1.25%). This cell population has an important role in immune tolerance to self-antigens as well as in homeostasis of the immune system.[16] Interestingly, in patients with autoimmune thyroiditis, the level of T reg lymphocytes is decreased to 5.3% in comparison with healthy controls who have a level of about 16%.[16] Diverse regulatory T cell subsets exist in the peripheral blood of patients with autoimmune diseases. Some of them have disturbed suppressive function, whereas other lymphocytes, although showing regularity, were without functional effects, probably owing to resistance of the appropriated target cells. Another interesting possibility is that once the immune tolerance is broken, and the inflammatory destructive phenomenon is ongoing, the activity of effector T cells would overcome the suppressive effect of T reg cells.

Engelan *et al*[11] and Arbeiter *et al*[17] mentioned a few cases of red blood cell aplasia after using MMF for patients who had undergone renal transplantation. MMF treatment in our patient induced complete recovery of PRCA. Furthermore, this drug did not alter the course of at least one of the endocrinopathies, as progression to primary ovarian failure and exocrine pancreatic insufficiency ensued over the 3 years of treatment. These data are in agreement with the results of Ward *et al*.[9] They treated the patient having APECED with oral CyA, and succeeded in treating gastrointestinal dysfunction, alopecia universalis and keratoconjunctivitis, and the progression of primary ovarian and adrenal failure.

The present case of a young woman, with associated autoimmune disorders (acquired PRCA and APECED homozygotic for the common R257X mutation of AIRE gene), showed excellent response of anaemia to MMF treatment, without toxicity and with complete haematological recovery, but unfortunately with progression of endocrinopathy.

This paper showed the significant role of γδTCR+ cells in PRCA, with a possibility that these cells were involved in pathogenesis of the disease. A significant decrease in the γδTCR+ cell count after 2 years of MMF treatment was associated with normal haematological findings, but without elimination of their monoclonal pattern.

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Milena Bakrac
Institute of Hematology, Clinical Center of Serbia, Belgrade, Serbia

Vladimir Jurisic
Institute for Pathophysiology, School of Medicine, University of Kragujevac, Kragujevac, Serbia

Tanja Kostic
Institute for Molecular Genetics and Genetic Engineering, Belgrade, Serbia

Vera Popovic, Sandra Pekic
Institute of Endocrinology, Clinical Center of Serbia, Belgrade, Serbia

Nada Kraguljac, Milica Colovic
Institute of Hematology, Clinical Center of Serbia, Belgrade, Serbia

Correspondence to: Professor V Jurisic, University of Kragujevac, School of Medicine, PO Box 124, 34 000 Kragujevac, Serbia

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Metastatic renal oncocytoma

Renal oncocytomas are classified as benign renal neoplasms in the 2004 *World Health Organization classification of renal tumours*.[1] Cases of metastatic tumours have been documented,[2–4] but subsequent reports have identified subtypes of renal tumours having similar histological morphology but having malignant potential. These tumours have been classified as either eosinophilic variants of renal cell carcinoma (RCC) or chromophobe carcinomas. Differentiating these tumours from oncocytomas has proved to be difficult and relies on a combination of histological morphology, immunohistochemistry and electron microscopy. There is still a presumption that if metastasis occurs then the tumour should not be classified as a renal oncocytoma and should be called an eosinophilic RCC.

We present a patient who presented with liver metastasis 9 years after the removal of a renal oncocytoma.

Case report

A woman in her 70s presented with left-sided abdominal pain. She was noted to have a mobile mass in the left upper quadrant. Baseline blood examinations were normal and she had no other significant medical history. An abdominal ultrasound was suggestive of a left RCC. A CT scan showed a 12 cm renal mass extending just across the midline, arising from the upper anterior part of the left kidney (fig 1). The left renal vein, liver and lymph nodes appeared unaffected. The conclusion was that this was most probably an RCC, but the pattern of enhancement was suggestive of a renal oncocytoma. A chest *x* ray was clear.

She underwent a left radical nephrectomy and adrenalectomy en bloc. There was no involvement of adjacent organs. She made an uneventful recovery. She remained well on follow-up, with normal renal function and full blood counts. She was discharged from follow-up 18 months after surgery.

After 9 years she re-presented with left-sided abdominal pain, bloating and nausea, but no vomiting. A chest *x* ray was normal and an abdominal *x* ray showed faecal loading; this was thought to be diverticular disease. An abdominal CT scan showed multiple liver masses.

An ultrasound-guided liver biopsy was performed.

A CT scan 4 months later showed multiple lesions throughout the liver, which enhanced in the arterial phase, consistent with multiple hypervascular metastases (fig 1). The tumours appeared much the same as on the previous scan. Her liver function tests were normal. She had few symptoms, consisting of some tiredness, minor weight loss but a good appetite until 18 months after she re-presented when she developed confusion. A CT scan of her head showed acute left parietotemporal haemorrhage with intraventricular extension, but there was no evidence of metastatic tumour. She remained an inpatient for 4 months during which her renal and liver function tests were normal. She was discharged to a nursing home where she died a week later. A post-mortem examination was not carried out.

Pathology

The renal tumour was in the upper and mid-zones of the kidney and measured up to 12 cm in diameter. The tumour was yellow–brown in colour with a central white stellate scar, 1.5 cm in diameter. The perinephric fat, renal vein and adrenal gland were uninvolved. Histology showed packets of regular cells with eosinophilic cytoplasm and occasional highly cellular trabecular areas (fig 2). There was no cellular atypia, and mitotic figures were not seen (0 per 1 mm^2). MIB-1 labelling index was $<1\%$. Hales colloidal iron was negative. The conclusion was that this was a renal oncocytoma.

The liver biopsy specimen showed cores of liver parenchyma with well defined islands of oncocytic cells arranged in nests (fig 3). The original renal tumour was reviewed in light of

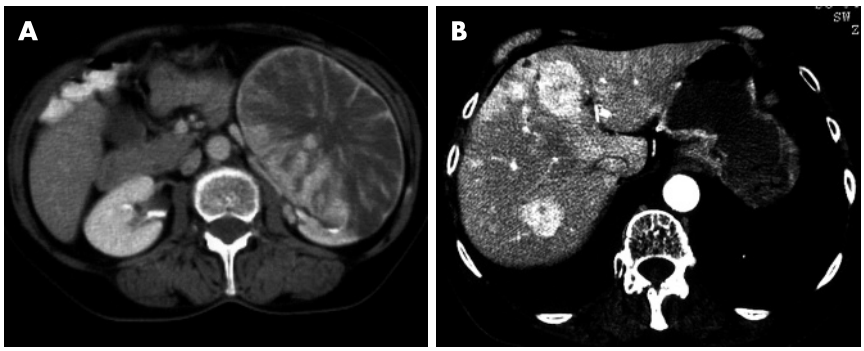

Figure 1 Enhanced CT scans showing (A) a 12 cm well-defined left renal mass with a central scar and radiating area of low density suggestive of oncocytoma and (B) the liver metastases that appeared 9 years later.