

CASE REPORT

Transient ischaemic attack secondary to paraneoplastic erythrocytosis

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SUMMARY

A 67-year-old woman with a history of hypertension and type 2 diabetes mellitus was admitted to the hospital due to aphasia and left-sided hemiparesis during the past 5 h with resolution of symptoms within 24 h. On admission laboratory analysis showed haemoglobin 19.2 g/dL and haematocrit 55.1%. Cerebral CT scan was also performed on admission revealing periventricular leucoaraiosis. Studies to investigate the cause of erythrocytosis were started and elevated erythropoietin levels were found. In order to investigate a secondary cause of erythrocytosis an abdominal ultrasound was conducted revealing a left renal mass. CT scans of thorax, abdomen and pelvis confirmed renal mass 8×8 cm of diameter, suggestive of neoplasm without associated lymphadenopathy or metastases. Radical nephrectomy was performed and a pathological diagnosis demonstrated clear cell renal cell carcinoma and was staged as T2aN0M0.

BACKGROUND

Transient ischaemic attacks (TIAs) are brief episodes of stroke symptoms with a duration less than 24 h. Symptoms result from an occluded blood vessel which soon reopens allowing neurological function to be restored. Although neurological symptoms desist, in 15–40% of TIAs brain infarcts do occur. Furthermore, emergency assessment is required since TIAs may herald stroke.¹ The aetiologies of TIAs are the same as ischaemic stroke, being mainly due to thrombosis and embolic occlusion, and less frequently, due to hypercoagulable disorders, vasculitis, underlying cardiomyopathy, vasospasms, drug abuse, etc.¹ Blood disorders have been implicated in 5–10% of ischaemic strokes and screening is included for patients with new onset of neurological symptoms.²

Erythrocytosis is a blood disorder characterised by elevated haematocrit (Ht) more than 48% in women and 52% in men, or elevated haemoglobin (Hb) greater than 16.5 g/dL in women and 18.5 g/dL in men.³ Patients are generally asymptomatic, but the symptoms they may experience are related to ischaemia from hyperviscosity and thrombosis caused by increased red cell mass. General symptoms may include fatigue, weakness and dyspnoea. Peripheral ischaemia may affect extremities and digits even causing erythromelalgia. Other signs and symptoms include mesenteric ischaemia, hepatosplenomegaly, ascites, headache, vertigo, tinnitus and impaired mental acuity.¹ Renal cell carcinoma (RCC) occurs in 1–5% of cases and is secondary to the

overproduction of erythropoietin. It forms part of the differential diagnosis, being one of the solid tumours most commonly associated with this phenomenon.³

Worldwide death rate due to RCC is estimated to be 100 000 deaths/year.⁴ Important risk factors include smoking which is implicated in up to 30% of cases,^{5–7} exposure to cadmium and asbestos, obesity, and acquired polycystic disease in patients with chronic kidney disease. Chromosomal abnormalities of the short-arm of chromosome 3 and gain of chromosome 7 have been identified in clear cell RCC.^{8–12}

CASE PRESENTATION

A 67-year-old woman with a history of arterial hypertension diagnosed 5 years previously, treated with enalapril 10 mg/day, and type 2 diabetes mellitus diagnosed 1 year ago, controlled by diet, was presented to the emergency room due to aphasia and left-sided hemiparesis 5 h prior to evaluation for which she was admitted to the hospital. The patient's family members reported that the patient had progressive short-term and long-term memory loss in the past 2 months, as well as *marche à petits pas* gait and urinary incontinence during the last month. The patient had no history of smoking or exposure to toxins.

On physical examination, the patient presented an arterial blood pressure of 160/110 mm Hg, BM test 142 mg/dL, SO₂ 95%, Glasgow Coma Scale (GCS) 9/15 points, deviation of the right corner of the mouth, involuntary movements were absent, non-fluent aphasia was present, pupils were isochoric and reactive to light, optic fundi were normal, no heart murmurs were present, pulmonary auscultation was normal, abdomen was normal, muscle strength in left limbs was decreased and graded as 3/5, whereas right limbs were normal with muscle strength graded as 5/5, deep tendon reflexes in left limbs were graded as 3/4 and right limbs were graded as 2/4, and finally a left plantar extensor response was present.

While hospitalised, the hemiparesis and aphasia resolved within 24 h and GCS score improved to 13/15 points.

INVESTIGATIONS

Investigations on admission

Creatinine 1.1 mg/dL, blood urea nitrogen 23 mg/dL; full blood count showed erythrocyte count 6.19 (reference value: 4.04–6.10×10⁶/mm³), leucocyte 8.0×10³/mm³, Hb 19.20 g/dL, Ht 55.10%, platelets



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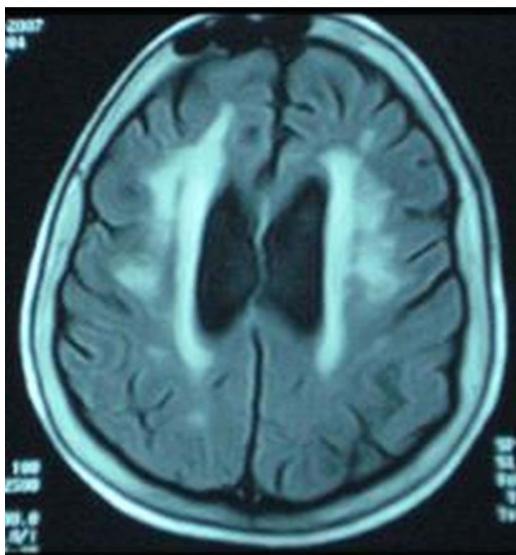


Figure 1 MRI of the brain showing multiple subcortical, periventricular, bilateral frontoparietooccipital and bilateral juxtacortical frontoparietal hyperintensities.

240 ($10^3/\text{mm}^3$), and erythrocyte sedimentation rate 56 mm/h. The patient had a normal chest radiograph. Cerebral CT scan was performed which showed areas of cerebral leucoaraiosis as well as in brain MRI which showed multiple subcortical, periventricular, bilateral frontoparietooccipital, and bilateral juxtacortical frontoparietal hyperintensities (figure 1).

Control laboratories were performed and full blood count results showed an erythrocyte count $7.17 \times 10^6/\text{mm}^3$, Hb 20 g/dL, Ht 62.30%; simple urine test was normal; arterial blood gases were normal. Studies for erythrocytosis were initiated, considering the cause of the TIA to be due to hyperviscosity. Erythropoietin level was 47 (reference value: 0–19 mU/mL). A peripheral blood smear reported erythrocytosis of undetermined aetiology. Spirometry results were normal. Transthoracic echocardiography findings included hypertensive heart disease, normal valves, without evidence of pulmonary hypertension. Carotid Doppler was normal. Tumour markers, including CYFRA21-1, CEA, β -hCG, CA 19–9, CA 15–3, α -fetoprotein and enolase, were normal. Despite normal tumour marker levels, there was suspicion of RCC and renal ultrasound was performed, finding a normal right kidney and an enlarged left kidney with distorted configuration due to the presence of two heterogeneous images located at the lower pole.

CT of thorax, abdomen and pelvis reported an enlarged left kidney with evidence of complex lesions having solid and liquid areas in connection with necrotic areas (figure 2).

DIFFERENTIAL DIAGNOSIS

- Hypoxaemia (secondary to toxin exposure, chronic lung disease, congestive heart disease)
- Polycythaemia vera
- Von Hippel-Lindau disease
- Hepatocellular carcinoma
- RCC

TREATMENT

On admission, acetylsalicylic acid 100 mg per orally four times a day and enoxaparin 40 mg subcutaneously four times a day were started. After diagnosis of RCC was made, the patient was



Figure 2 CT of the abdomen and pelvis reporting an enlarged left kidney with evidence of complex lesions having solid and liquid areas in connection with necrotic areas. Mass measuring 8×8 cm to consider neoplasia.

taken to the operating room where the left renal mass with necrotic tissue in absence of metastasis was visualised and left nephrectomy was performed (figures 3 and 4). The pathology report was consistent with clear cell RCC (figures 5 and 6).

OUTCOME AND FOLLOW-UP

Follow-up after radical nephrectomy with laboratory analysis monitoring Hb and Ht was conducted 2 months later with results of 14 g/dL and 35%, respectively. Urinary incontinence was resolved without recurrence after 1 year and follow-up of Hb and Ht continued to show normal results. As for the memory disturbances no improvement was observed.

DISCUSSION

The patient was brought to the emergency room because of new onset of neurological symptoms indicative of cerebrovascular disease. Initial cerebral CT scan ruled out cerebral haemorrhage. Further studies were warranted in assessing a possible ischaemic stroke and as symptoms resolved within 24 h the diagnosis of TIA was made retrospectively. A routine full blood count revealed a significant increase of red cell mass. The hyperviscosity associated with increased red cell mass made erythrocytosis a possible aetiology of the TIA in this patient.

The clinical history of any patient with erythrocytosis is very important for a guided diagnosis. The most frequent cause of erythrocytosis is hypoxaemia induced by pulmonary disease, usually manifesting as chronic cough, dyspnoea and cyanosis.



Figure 3 Nephrectomy with evidence of necrotic areas.



Figure 4 Macroscopic study in the lower pole revealing a nodule about 8 cm in diameter, yellowish-brown colouration.

Other common causes include smoking, chronic exposure to carbon monoxide, obstructive sleep apnoea syndrome, cobalt poisoning, and living at high altitudes for prolonged periods of time. In the presence of increased red cell mass and splenomegaly, polycythaemia vera should be suspected.¹³ Other causes are haemoglobinopathies, Rendu-Osler-Weber syndrome due to the presence of pulmonary arteriovenous malformations. Drug-induced causes may include the use of androgens, anabolic steroids and erythropoietin injections.

While investigating the cause of erythrocytosis in this patient, spirometry and arterial blood gases were performed, both with normal results, making hypoxaemia and lung disease improbable. The patient has an underlying heart disease, as demonstrated by transthoracic echocardiography, secondary to a 5-year history of treated hypertension, nevertheless these results ruled out congestive heart failure and pulmonary hypertension, making the underlying heart disease in the patient an improbable cause of erythrocytosis. During the physical examination of the patient splenomegaly was not detected, making polycythaemia vera an improbable diagnosis. Furthermore, the social history of the patient was not suggestive of an occupation-related origin; to the contrary, carboxyhaemoglobin levels would have been taken.¹³

After hypoxic and occupational causes were ruled out the following approach to study the cause of the patient's erythrocytosis was to measure serum erythropoietin levels. If serum erythropoietin levels were low and the patient had presented splenomegaly, thrombocytosis, leucocytosis and arterial oxygen saturation at or above 92%, polycythaemia vera would have been the most probable cause of primary erythrocytosis. If serum erythropoietin levels were normal, bone marrow biopsy

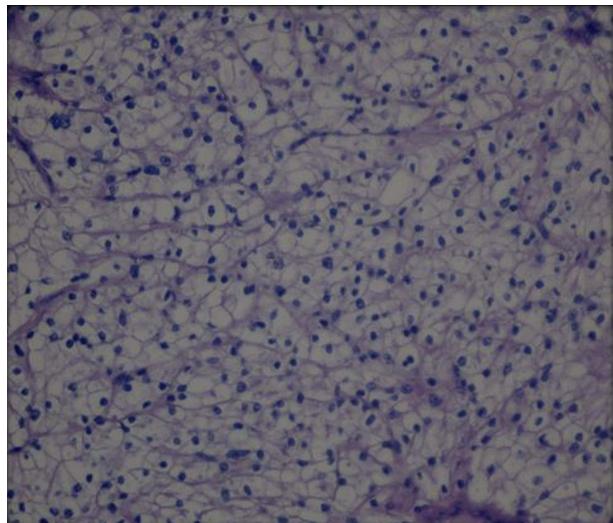


Figure 6 Cytological detail of a clear cell renal carcinoma cell showing low grade.

would have been performed to complement the diagnosis of polycythaemia vera. In the case that the bone marrow biopsy would have been inconclusive, analysis to identify JAK2 mutations may have been conducted; where a positive result would imply the diagnosis of a chronic myeloproliferative disorder including polycythaemia vera, and a negative result would require the analyses to be repeated 3 months later.¹³ Elevated serum erythropoietin levels imply secondary erythrocytosis, as in the presented case.

One of the causes of secondary erythrocytosis is von Hippel-Lindau disease. This disease is an autosomal dominant disorder characterised by the predisposition to several kinds of cancers, including clear cell RCC, cerebellar haemangioblastomas, pheochromocytoma, retinal angiomas, and renal and pancreatic cysts. Up to one-third of these patients develop RCC. Tumours that have been associated with vHL gene mutations are often hypervascular and may cause erythrocytosis due to overproduction of red blood cells secondary to increased vascular endothelial growth factor and erythropoietin.¹⁴ About 25% of patients at the time of diagnosis present metastases or locally advanced lesions.¹⁵ Diagnosis is made when two or more von Hippel-Lindau tumours are detected, or one tumour with a positive family history for von Hippel-Lindau disease. Specific genetic testing with Southern blot and gene sequencing may be performed in patients who do not satisfy clinical diagnostic criteria.¹⁶

Tumours that are often associated with secondary erythropoietin overproduction are hepatocellular carcinoma, RCC, pheochromocytoma and haemangioblastoma.¹⁷

RCC originates in the epithelium of the proximal convoluted tubule of the nephron.¹⁸ RCC is more common in males and is usually diagnosed between the fifth and seventh decade.¹⁹

For its wide range of symptoms RCC has been named the "internist's tumour". The classic triad, or *Guyón's triad*, of flank pain, haematuria and palpable mass occurs in less than 10% of cases and when present is associated with advanced disease. Haematuria is observed when a renal tumour has invaded the collecting duct.²⁰⁻²² Unlike glomerulonephritis, haematuria in RCC may cause blood clots. Most patients who are diagnosed with RCC consult because of haematuria.¹⁹ During physical examination a palpable mass may be found, especially when the mass is associated with a tumour of the

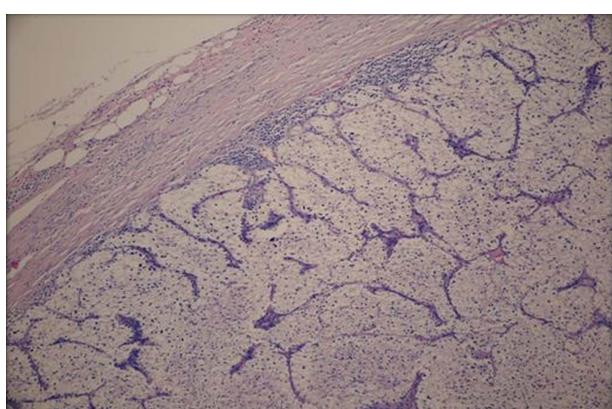


Figure 5 Histological view of clear cell carcinoma.

lower pole.²³ When left-sided varicocele is present a renal tumour that obstructs the gonadal vein should be ruled out. When ascites is present due to hepatic outflow obstruction, Budd-Chiari syndrome should be considered as a secondary manifestation of RCC.²³

Many patients with clear cell RCC present paraneoplastic symptoms.²⁴ This is due to altered production of various hormones produced by the kidney, including erythropoietin.²⁴ Normocytic and microcytic anaemia have been reported in up to 88% of patients with advanced disease.^{24 25} Weight loss and fever are also common symptoms. Liver dysfunction can occur without metastasis in clear cell RCC, a constellation of symptoms known as Stauffer syndrome. In some cases regression of liver dysfunction is reported when nephrectomy is performed.²⁶ Hypercalcaemia has been reported in up to 15% of cases.²⁷ The treatment of choice for hypercalcaemia in patients with metastatic bone disease is a biphosphonate.²⁸ There have been reports of secondary amyloidosis in about 3% of patients.²⁹ Polymyalgia rheumatica has been associated as a very rare event, which has a poor response to prednisone and clinical improvement after nephrectomy.³⁰ Thrombocytosis is rare but its presence is indicative of poor prognosis.³¹

When suspecting a renal neoplasm, abdominal CT scan and ultrasonography are the diagnostic methods of choice. An abdominal CT with contrast medium will display a renal tumour as a heterogeneous image. An MRI with gadolinium is the most appropriate study when there is tumour invasion into the inferior vena cava, but currently the use of gadolinium in MRI is of special concern due to the risk of nephrogenic systemic fibrosis in patients with glomerular filtration rate <30 mL/min/1.73 m².³² In the presence of metastases an F-18 fluorodeoxyglucose-positron emission tomography is a supportive study, but its sensitivity is low when the lesions are less than 1 cm. Metastasis occurs mainly in the lungs in about 60% of cases.³³

Pathological diagnosis is preferably established by tumour removal, as percutaneous needle biopsy is less accurate. Currently, five histological subtypes of renal carcinoma have been identified, of which clear cell RCC is implicated in about 75% of cases.^{15 34 35} Prognosis of RCC depends on tumour size, stage, grade and necrosis.

Surgical treatment with radical nephrectomy has been shown to increase survival rates up to 90% at 5 years when RCC is detected at an early stage.³⁶ Partial nephrectomy is considered in monorenal patients with tumours smaller than 4 cm.³⁷ The reappearance of erythrocytosis after surgery with curative intent should cause alarm and recurring disease should be ruled out.³

With current knowledge of molecular pathogenesis, antiangiogenic therapy may be used. Based on analysis of the VHL gene, its abnormalities have been associated with an overproduction of vascular endothelial growth factor and increased tumour angiogenesis.³⁸ This principle has been employed in clear cell RCC treatment as drugs such as sunitinib, sorafenib, pazopanib and bevacizumab are believed to block the vascular endothelial growth factor pathway by binding to circulating vascular endothelial growth factor and preventing the activation of the vascular endothelial growth factor receptor.³⁸

In relation to the use of phlebotomy in the management of acute ischaemic stroke the clinical practice guideline (CPG) of the American Heart Association and American Stroke Association published in 2007 says that the current data indicate that phlebotomy did not reduce mortality or improve functional outcome in patients who survive, but it adds that the only possible exception for use in these patients would be the presence of severe polycythaemia.

No information on how soon surgery is needed to make before that deficits are permanent.

Learning points

- ▶ Transient ischaemic attacks are frequent in emergency rooms and non-neurological causes must always be suspected.
- ▶ Clear cell renal cell carcinoma is often presented with paraneoplastic phenomena and its early diagnosis greatly influences the prognosis of patients.
- ▶ Secondary erythrocytosis due to renal cell carcinoma usually subsides after performing radical nephrectomy of the affected kidney.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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