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Case report

Successful treatments of polyarteritis nodosa cerebral vasculitis and recurrent *Elizabethkingia meningoseptica* septicaemia in a dialysis patient

Nestor Velasco,[1] Sital Karki,[2] Oscar Rafael Tenreiro[1,3]

[1]Renal Medicine, Treetop Hospital, Hulhumale, Maldives
[2]Department of Renal Medicine, Treetop Hospital, Hulhumale, Maldives
[3]Department of Radiology, Treetop Hospital, Hulhumale, Republic of Maldives

Correspondence to
Dr Nestor Velasco;
nestorvelasco@hotmail.com

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SUMMARY

We report a case of cerebral vasculitis in a 31-year-old woman who presented with chronic kidney disease stage 5, labile hypertension and severe headaches. The diagnosis of cerebral vasculitis made on magnetic resonance angiography (MRA) and late diagnosis of polyarteritis nodosa were made by conventional CT angiography. Immunosuppression was complicated by recurrent septicaemia due to *Elizabethkingia meningoseptica*. Treatment of the vasculitis resulted in marked improvement of MRA appearances, headaches and anxiety and stabilisation of blood pressure. The septicaemia required parenteral quinolone treatment and oral cotrimoxazole.

BACKGROUND

This case highlights the problems of the late diagnosis of polyarteritis nodosa (PAN) caused by relying only on serological tests and histology, while middle-sized arterial vasculitis is more reliably diagnosed by angiography. Furthermore, renal angiography or CT angiography (CTA) should have been part of the workup of chronic and uncontrolled hypertension.

Rare cases of transient insulin requiring diabetes mellitus do happen like in this case with pancreatic involvement by PAN.

Rare multiresistant infections like septicaemia caused by *Elizabethkingia meningoseptica* require specific treatment and careful follow-up in immunosuppressed patients.

CASE PRESENTATION

We first saw this 31-year-old woman when she presented to the emergency room on 2 December 2018 with complaints of years of severe headaches and frequent vomiting and 2 days of left lower back pain. The patient was afebrile, with blood pressure of 194/112 mm Hg, pulse rate of 86 beats/min, respiratory rate of 14 breaths/min and O_2 saturation of 99% on room air. She had pale conjunctiva and normal jugular venous pulse and no signs of overhydration, with clear breath sounds and no heart murmurs. Laboratory studies revealed a random blood glucose level of 140 mg/dL, white blood cell count of 11 600 cells/mm^3, with 66.5% neutrophils, haemoglobin unit of 105 g/L and platelet count of 487 000/μL. Serum sodium was 134 mmol/L, with potassium of 3.2 mmol/L, urea of 200.3 mg/dL, uric acid of 10.1 mg/dL, creatinine of 8.58 mg/dL, estimated glomerular filtration rate (eGFR) of 5.8 mL/min, corrected calcium of 6.01 mg/dL and phosphorus of 6.53 mg/dL. Urine analysis showed 3+ protein with 2+ leucocytes and 1+ blood. Urine culture revealed no growth. Intact parathormone was 636 pg/mL. The patient had a serum iron level of 27 μg/dL and a vitamin D level of 19.4 ng/mL. Chest X-ray revealed cardiomegaly; abdominal ultrasound examination showed small kidneys with increased cortical echogenicity and poor corticomedullary differentiation. The right kidney measured 7.8×4×4 cm and the left kidney measured 8×3×4 cm, which was suggestive of chronic renal parenchymal disease. The patient was very unwell and emergency dialysis was done after insertion of a catheter in the right internal jugular vein.

Records of her medical history revealed she had been investigated for delayed menarche and infertility and was diagnosed with diabetes mellitus in 1997, and she was treated with metformin and then relatively high doses of insulin (average 50 units per day) for 2 years.

Spontaneously, by the year 2015, her blood sugars had become normal and she was no longer treated with insulin or metformin with glycosylated haemoglobin of 5.6% in 2015 and 6.1% in 2017. She had frequent headaches and vomiting. Proteinuria was never higher than 393 mg/24 hours. Uric acid increased at 9.7 mg/dL and parathyroid hormone increased at 1159 pg/mL. A renal biopsy was done in Sri Lanka in the year 2016, which was reported as showing only nephrosclerosis. Serum complement levels were normal and antineutrophil cytoplasmic antibodies (ANCAs) were negative. She had severe hypertension, with blood pressures reaching 240/130 mm Hg with occasional lower readings not controlled on metoprolol, clonidine, nicardipine, amlodipine and losartan. ECG revealed left ventricular hypertrophy. By February 2017, she was still complaining of headaches, and she had a brain MRI scan that was reported as showing an old basal ganglia infarct. Investigations also included normal 24-hour urine for catecholamines, normal cortisol levels, elevated serum aldosterone level at 66 ng/dL and elevated renin at 14.4 μIU/mL. Renal function deteriorated over the next 2 years from a serum creatinine of 1.3 mg/dL (eGFR 56 mL/min) in 2015 to a serum creatinine of 3.8 mg/dL in January

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2017 when her eGFR was 15 mL/min. She was considered for dialysis and a creation of arteriovenous fistula was done without success. By January 2018, the patient's eGFR had decreased to 8 mL/min.

After her admission to our centre in December 2018, her blood pressures remained elevated and highly variable in the same day from 200/120 mm Hg to 126/67 mm Hg, this also being present on home readings and during sessions of haemodiafiltration. Repeated bioimpedance measurements with Fresenius body composition monitor showed her to be in normal hydration or mildly dry. Severe headaches and vomiting accompanied the first weeks of dialysis. CT of the brain showed multiple areas of old infarctions in both basal ganglia affecting the head of the caudates and both putamen nuclei in the lenticular striate vascular distribution (figure 1). A suspicion of vasculitis was confirmed with MRI, where angiography of the brain revealed multifocal significant stenosis of the supraclinoid internal carotid artery, anterior cerebral artery/A1 segments and middle cerebral artery/M1 segments bilaterally, suggestive of vasculitis and multiple bilateral and haemorrhagic infarctions in the basal ganglia (figure 2).

Speckled antinuclear antibodies were positive at a low titre of 1:40; lupus anticoagulant was present but sample taken after days of exposure to anticoagulation for dialysis. Anticardiolipin IgG and IgM antibodies were negative and cryoglobulins were negative too. Serology for hepatitis B and hepatitis C and for HIV I and II were negative.

Treatment was commenced with three daily doses of intravenous methylprednisolone 500 mg followed by oral prednisolone 60 mg daily. There were problems with adherence to this regime at home despite supervision by her relatives. Cyclophosphamide was not ready available and the patient was started on mycophenolate mofetil 2 g daily. Unfortunately, the patient developed severe diarrhoea and mycophenolate was stopped. She was commenced on rituximab 1 g intravenously, which was repeated after 2 weeks, and continued with the prednisolone. In between, the patient had one episode of shivering but remained afebrile. C reactive protein (CRP) increased to 2.92 mg/dL (normal range<0.5).

Blood cultures were done, and before results were available, intravenous vancomycin and gentamycin were given after each dialysis. Blood cultures grew *E. meningoseptica*, which was resistant to both vancomycin and gentamycin but sensitive to ciprofloxacin, which was commenced orally at 500 mg two times per day for 10 days. After completion, a subsequent set of blood cultures again grew *E. meningoseptica*, and we decided to treat her with parenteral levofloxacin and oral cotrimoxazole, after which blood cultures became negative and CRP normalised to 0.44 mg/dL. There was a remarkable improvement of headaches with no further vomiting, and the patient was generally less anxious, with blood pressures also becoming more stable, ranging from 165/97 to 142/88 mm Hg. A second magnetic resonance angiography of the brain revealed significant improvement

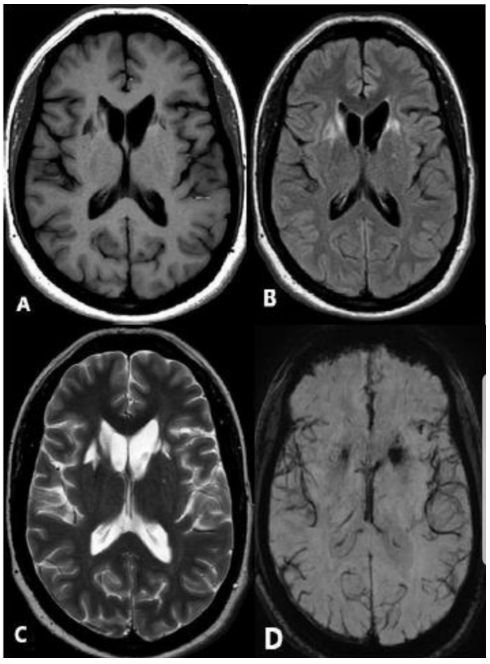

Figure 2 MRI of the brain in multiple sequences without contrast in T1W (A), FLAIR (B), T2W and DWI (D) axial images show areas of old infarction in the basal ganglia affecting the head of the caudates and putamen nuclei with central encephalomalacia and surrounding astrogliosis. There is an associated profound abnormal gradient blooming artefact in the SWI sequence, which suggests associated old haemorrhages. DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging; T1W, T1-weighted; T2W, T2-weighted.

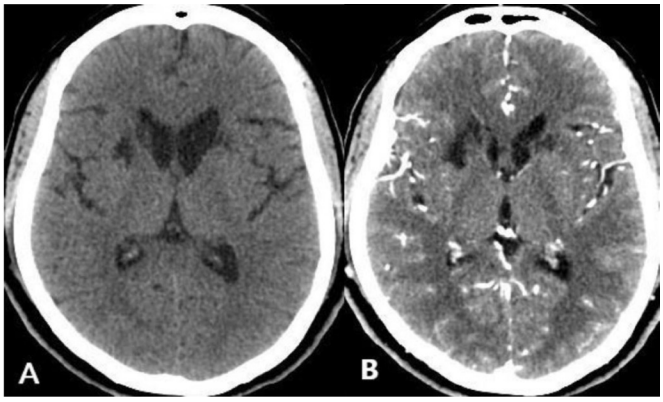

Figure 1 CT of the brain without (A) and with (B) contrast shows multiple areas of old infarctions affecting both heads of the caudates and putamen nuclei in the lenticular striate vascular distribution bilaterally.

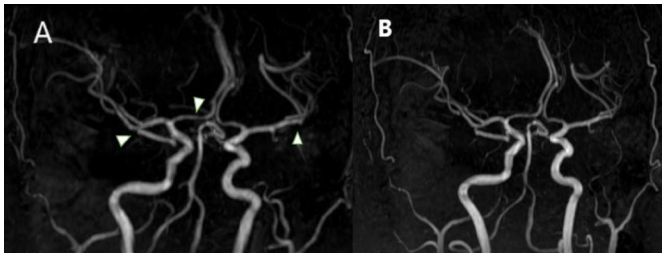

Figure 3 MRA TOF sequence without contrast after the patient admission (A) shows evidence of multifocal significant luminal stenosis with a beaded-like appearance affecting both ACA/A1 and MCA/M1 segments bilaterally. In addition, areas of stenosis in both proximal M2 segments and severe focal stenosis of the left PCA/P1 segment are identified (arrowheads). The MRA 3 months after treatment (B) shows significant improvement of the beaded-like narrowing appearance and the multifocal areas of stenosis seen in the anterior circulation since the last study. Persistent stenosis is seen in the posterior circulation/left P1 segment (arrowheads). ACA, anterior cerebral artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; TOF, time-of-flight.

(figure 3), and a conventional CTA of the renal and mesenteric arteries was diagnostic of PAN, with major involvement of both kidneys and pancreas (figure 4).

OUTCOME AND FOLLOW-UP

Over the last 3 months, this patient has improved greatly with well-controlled hypertension and no headaches or vomiting. The patient remains on regular dialysis (haemodiafiltration) three times a week and is considering future renal transplantation.

DISCUSSION

E. meningoseptica is a newly recognised Gram-negative pathogen causing septicaemia and is usually resistant to many antibiotics.[1] It can be associated with significant morbidity and mortality and occasionally asymptomatic. It has been described in the context of both haemodialysis and immunosuppression.[2 3] In our patient, there was a need for continuing intensive immunosuppression with rituximab despite the presence of *E. meningoseptica* septicaemia that was successfully treated, although in retrospect, we should have not have used the oral ciprofloxacin but the parenteral form in the initial treatment.

PAN is a rare medium-sized arteritis with an estimated incidence of 4.4–9.7 cases/million[4] that has been recognised to both produce renal impairment with associated severe hypertension[5 6] and involve various other organs including the pancreas.[7 8] Both of these situations were present in our patient, who had typical aneurysmal arteritis in these territories (see figure 4). We postulate that this patient had PAN for many years, and the unusual transient insulin requiring diabetes that spontaneously disappeared was due to the PAN involvement of mesenteric and pancreatic arteries demonstrated by our angiography years later. This situation was previously described.[9 10] Infrequently, PAN can involve the brain arteries, which was also the case here and was associated with late disease.[11 12] High serum levels of both renin and aldosterone should have increased suspicion of PAN.[13] Unlike ANCA-positive vasculitis, PAN does not have an easy marker for activity, and a high level of suspicion is required for detecting symptoms of cerebral involvement. Treatment with immunosuppression is similar to other vasculitides,[14] and in cerebral vasculitis, rituximab has been one of the promising treatments.[15] Corticosteroids remain important in controlling disease activity, and rituximab regimes require less stringent issues of long-term adherence that could be a significant factor in these cases. Renal impairment due to PAN requires imaging of the arteries rather than renal biopsy[6 16] as glomerulonephritis is not usually associated with it, unlike small-vessel ANCA-positive vasculitis. Early diagnosis with arterial imaging is necessary if one is to prevent serious disabilities. Furthermore, untreated PAN will continue to produce severe organ dysfunction even years after producing end-stage renal failure, and immunosuppression is usually necessary to control the systemic disease and can be beneficial with rapid improvement, as shown in our case.

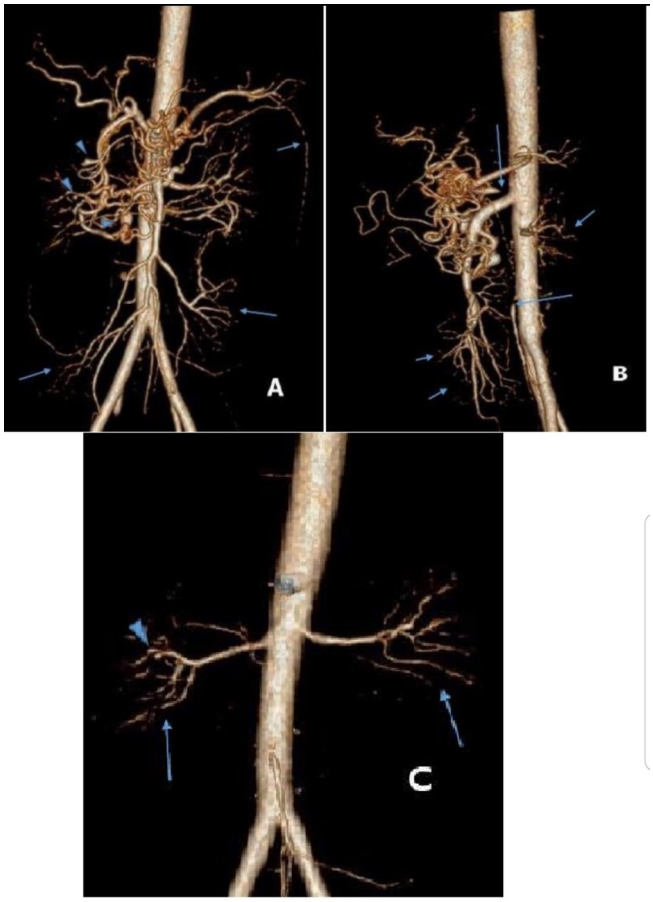

Figure 4 CTA of the abdominal aorta with three-dimensional reconstructions in anteroposterior and sagittal views show evidence of celiac trunk occlusion at the origin. Severe stenosis distal to the origin of the inferior mesenteric artery (large arrows). There is severe renal and mesenteric artery disease with thickening of the walls, moderate to severe diffuse multifocal narrowing associated with segmental dilatation (rosary-like appearance) predominantly affecting the distal renal branches. Multiple intraparenchymal renal branch microaneurysms (1 mm) are identified (small arrows). At least four aneurysms are identified in the anterior division of the right kidney and in the distal gastroduodenal branches adjacent to the head of the pancreas (arrowheads). All the angiographic findings suggest severe and long-standing medium-vessel and small-vessel primary vasculitis of the mesenteric and renal arteries consistent with polyarteritis nodosa. CTA, CT angiography.

Learning points

- Simultaneously elevated serum aldosterone and renin levels are markers for suspecting renovascular diseases like polyarteritis nodosa (PAN).
- Renal biopsy is not usually diagnostic of PAN since this disease is not accompanied by glomerulonephritis, and angiographic studies are needed.
- Magnetic resonance angiography can be used to monitor response to treatment in cerebral involvement of PAN.
- Vancomycin and gentamycin are not a suitable combination treatment for *Elizabethkingia meningoseptica* septicaemia, and blood cultures are essential to diagnose septicaemia in dialysis patients.
- Immunosuppression with rituximab is a good alternative treatment for patients with cerebral vasculitis that also facilitates adherence.

Twitter Sital Karki @sitalcoolk

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