European Journal of Case Reports in Internal Medicine

Invasive Pneumococcal Disease Associated with Fanconi-Like Syndrome

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Doi: 10.12890/2019_001230- European Journal of Case Reports in Internal Medicine - © EFIM 2019

Received: 24/07/2019
Accepted: 12/08/2019
Published: 27/09/2019

How to cite this article: Soh JXJ, Goh RKH, Zheng S. Invasive pneumococcal disease associated with Fanconi-like syndrome. *EJCRIM* 2019;**6**: doi:10.12890/2019_001230.

Conflicts of Interests: The Authors declare that there are no competing interest

ABSTRACT

Acquired causes of Fanconi syndrome in adults are usually due to drugs, toxins or paraproteinaemias. Infectious causes are rarely described. We report a case of invasive pneumococcal disease in a patient who developed a Fanconi-like syndrome during the course of her illness. This patient presented with multiple electrolyte derangements consisting predominantly of hypokalaemia, hypomagnesaemia and hypophosphataemia during hospitalization for invasive pneumococcal disease with possible Austrian syndrome. Further evaluation revealed significant urinary losses of these electrolytes, uric acid and β2-microglobulin. Together with evidence of hypouricaemia, this is suggestive of proximal renal tubulopathy, and hence a Fanconi-like syndrome. The patient's clinical condition and biochemical anomalies improved following pneumococcus treatment.

LEARNING POINTS

- Suspect Fanconi syndrome when there are multiple electrolyte derangements consisting of hypokalaemia, hypomagnesaemia and hypophosphataemia.
- Recognise the common causes of Fanconi syndrome and appreciate that infections such as legionellosis, leptospirosis and pneumococcal disease can potentially result in Fanconi syndrome.
- The management of Fanconi syndrome is generally supportive and involves treating the underlying cause.

KEYWORDS

Pneumococcus, *Streptococcus pneumoniae*, Fanconi syndrome, proximal renal tubulopathy

CASE DESCRIPTION

An 83-year-old woman presented with cough, fever and delirium secondary to invasive pneumococcal disease (IPD) and possible Austrian syndrome. Blood cultures grew *Streptococcus pneumoniae*. A lumbar puncture performed following antimicrobial therapy showed cerebrospinal fluid pleocytosis, raised protein and pneumococcal antigen (Alere BinaxNOW®) positivity. Her chest radiograph (*Fig. 1*) on admission revealed left lung consolidation. Multiple cortical and subcortical infarcts were seen on magnetic resonance imaging of her brain (*Fig. 2*), suggesting a cardioembolic source. Dysmorphic red blood cells were seen on urine phase contrast. Transthoracic echocardiography was negative for vegetation and she was too unwell to undergo transoesophageal echocardiography.

The patient's medical history included cervical cancer which had been treated with radiotherapy 3 years ago, without recurrence. Apart from simvastatin for dyslipidaemia, the patient was not taking any other medications, including over-the-counter or traditional medicines. Her previous serum electrolytes during routine follow-up were normal and there had been no hospitalization during the previous 3 years.

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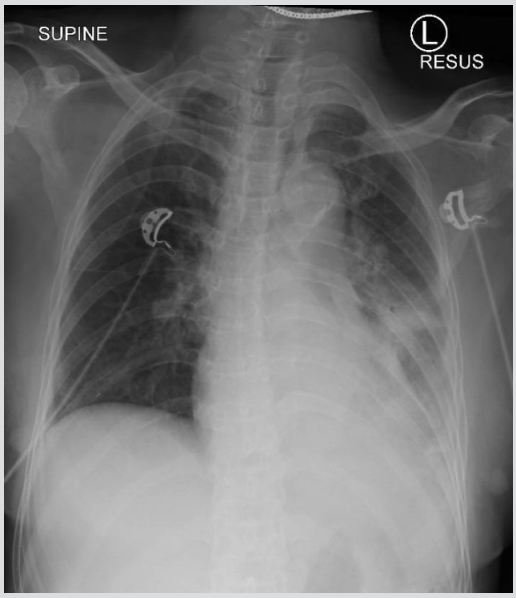
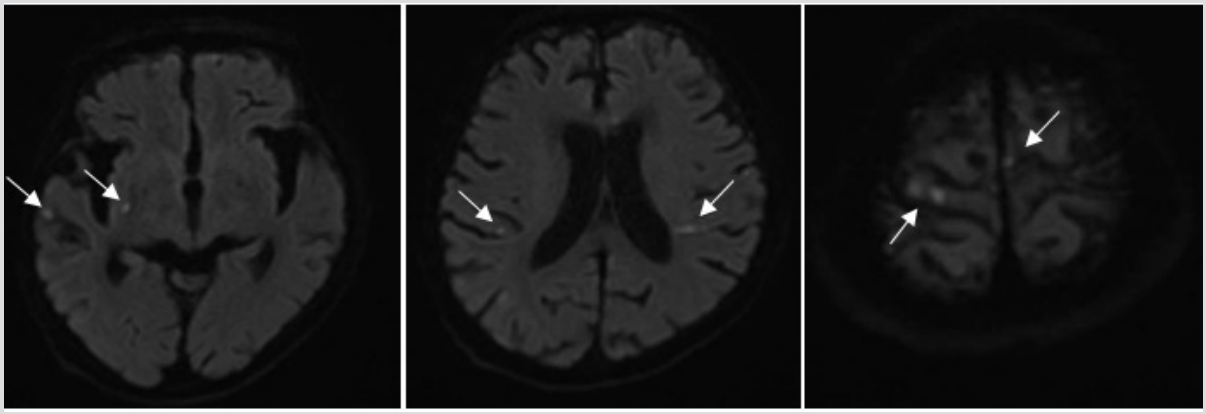


Figure 1. Patchy air-space opacities in the left mid and lower zones on chest radiograph

Figure 2. Scattered foci of restriction diffusion (white arrows) in bilateral cortical, subcortical and deep white matter regions on magnetic resonance imaging of the brain



The patient was treated with meningeal administration of parenteral antibiotics and completed 4 weeks of antimicrobial therapy (comprising ceftriaxone, stepped down to benzylpenicillin), in view of possible infective endocarditis, with clinical improvement. No corticosteroids were started.

Interestingly, the patient had hypokalaemia and hypomagnesaemia on presentation, without vomiting or diarrhoea. Of note, serum calcium/phosphate levels were normal on initial presentation. She only started developing hypophosphataemia on the 8th day of hospitalization. She continued to be hypokalaemic, hypomagnesaemic and hypophosphataemic despite aggressive initial replacement therapy, prompting further evaluation. Notably, the following urinary indices were raised: protein/creatinine ratio (1.53 mg/dl), spot potassium/creatinine ratio (12.83 mEq/mmol), 24-hour urine potassium (58 mmol/day), fractional excretion of phosphate (22.89%), fractional excretion of magnesium (14.37%), 24-hour urine magnesium (9.07 mmol/day), fractional excretion of uric acid (13.91%) and raised urine β2-microglobulin/creatinine ratio (3212 µg/g). These biochemistry results were consistent with proximal tubular urinary losses, and gradually resolved during treatment of the patient's underlying infection (*Table 1*). However, no acidaemia or glycosuria was present. There were no hypotensive episodes during her hospitalization and her serum creatinine remained in the normal range with maintenance of good urine output throughout hospitalisation.

A Fanconi-like syndrome was hence suspected, presumably related to invasive pneumococcal infection, given lack of a secondary cause and its resolution following antimicrobial treatment. The patient's drug history and exposures were unremarkable. Blood and urinary screens for monoclonal bands were negative. She did not have any stigmata of rheumatological disease and both antinuclear antibody and extractable nuclear antigen were negative. Serum vitamin D levels were found to be low on day 14 of hospitalization and replacement therapy was initiated. This is unlikely a familial cause as the patient is elderly and did not subsequently require long-term oral electrolyte replacement.

The patient's serum electrolytes had normalized by the time of her outpatient follow-up 1 week after antibiotic completion (*Table 1*).

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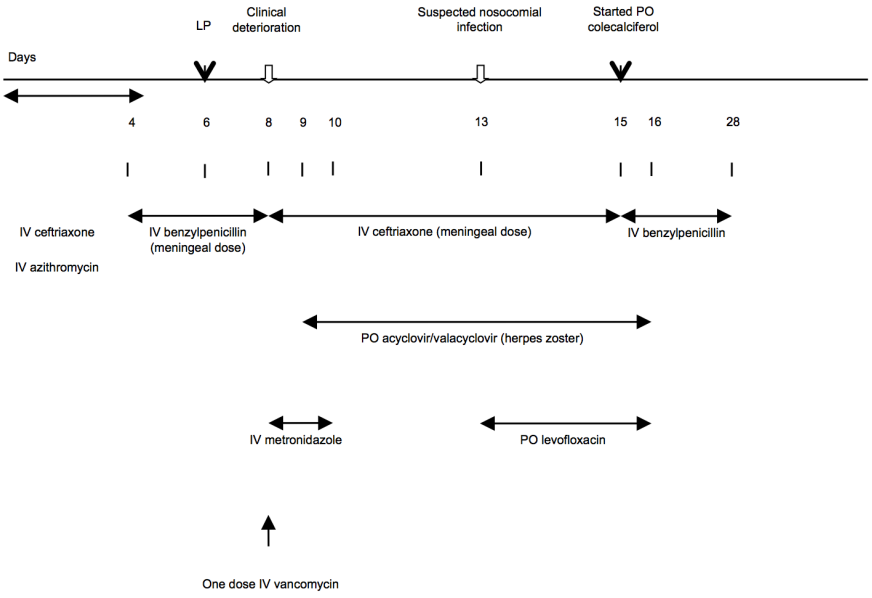
Day	1	6	10	12	13	14	21	35	47
Serum potassium (mmol/l) (3.5–5.1)	2.8 ↓	2.2 ↓	2.9 ↓	3.7	3.1 ↓	3.5	3.5	4.2	3.9
Serum magnesium (mmol/l) (0.74–0.97)	0.73 ↓		0.84	0.77	0.65 ↓	0.64 ↓	0.72 ↓	0.82	0.71* ↓
Serum phosphate (mmol/l) (0.94– 1.50)	1.11			0.91 ↓	0.81 ↓	0.89 ↓	1.08	1.30	1.05
Serum parathyroid (intact) hormone (pmol/l) (1.60–6.90)					8.65 ↑				
Serum 25 hydroxyvitamin D (µg/l) (20–100)						6 ↓			51
Serum uric acid (mmol/l) (143–330)					122 ↓				
FE of uric acid (%)					13.91 ↑				
Urine β2-microglobulin/creatinine ratio (µg/g)									
(26–260)					3212 ↑		712 ↑		617 ↑
Urine protein/creatinine ratio (mg/dl) (<0.2)		1.53 ↑							0.19
Urine potassium/creatinine ratio (mEq/mmol)			12.83 ↑				14.5 ↑		
24-hour urine potassium (mmol/day)					58				
FE of magnesium (%)				14.37 ↑			3.88		2.81
24-hour urine magnesium (mmol/day) (1.97–4.94)				9.07 ↑					
FE of phosphate (%)				22.89 ↑			10.56		9.63
Tubular maximum phosphate reabsorption				0.71 ↓			0.966		1.03
24-hour urine phosphate (mmol/day)									
(13.00–42.00)				26.04					
Urine pH (4.6–7.0)				7.0					
Urine glucose (dipstick)				Negative					
Progress and treatment history									

*Had gastrointestinal symptoms; repeat test 1 month later was 0.82 mmol/l.
Yellow box: replacement of electrolyte within 24 hours.
FE: fractional excretion; LP: lumbar puncture; IV: intravenous; PO: per os; ↑: increased, ↓: decreased.

Table 1. Serum, urinary results and antimicrobial therapy demonstrating progression and resolution of pneumococcal disease and Fanconi-like syndrome

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They remained normal without replacement therapy 7 weeks after her initial presentation of IPD. This further supports our suggestion that IPD occurred in association with this Fanconi-like syndrome, which resolved after treatment. Pre-existing idiopathic proximal tubulopathy is less likely in this case, given the previous normal serum electrolytes and evidence of complete resolution of tubulopathy after the acute infective episode.

DISCUSSION

Fanconi syndrome (FS) is caused by global dysfunction of the renal proximal tubule resulting in excessive urinary excretion of amino acids, glucose, phosphate, potassium, bicarbonate and uric acid[1]. This diagnosis should be considered when a patient presents with normal anion gap metabolic acidosis, hypokalaemia and urinary pH >5.3[2]. Acquired causes of FS in adults are shown in *Table 2*[1, 3].

Drugs: Aminoglycosides (gentamicin>tobramycin>amikacin), tetracyclines, nucleotide/nucleoside reverse transcriptase inhibitors (adefovir, tenofovir, cidofovir, didanosine, stavudine), sodium valproate, carbonic anhydrase inhibitors, azathioprine, chemotherapeutic agents (ifosfamide, cisplatin, carboplatin, imatinib), aspirin, deferasirox, fumaric acid, suramin
Toxic/metabolic causes: Heavy metal poisoning (cadmium, lead, mercury, copper), glue sniffing, Chinese herbal remedies containing Aristolochia species, vitamin D deficiency
Paraproteinaemias: Sjogren's syndrome, light chain proteinuria, multiple myeloma, amyloidosis
Others: Renal transplantation

Table 2. Causes of adult-onset Fanconi syndrome

Infective aetiologies are not thought to commonly cause proximal renal tubulopathy, although there have been reports of acquired FS in patients with Legionnaire's disease[4, 5]. In these cases, the patients presented with hypophosphataemia, hypokalaemia, hypouricaemia and/or hyponatraemia which resolved after the patients had recovered from Legionella pneumonia. Koda et al. reported elevated urinary β2-microglobulin in a patient, indicating severe renal tubular damage[5]. Kinoshita-Katahashi et al. speculated that direct infection by *Legionella pneumophila* in the proximal tubules disrupted mitochondrial function, resulting in FS[4]. Known to have a predilection for colonization in the proximal tubule, leptospirosis can also cause tubulointerstitial nephritis and proximal tubular dysfunction[6]. Tubular injury in these instances is believed to be mediated through Toll-like receptor-dependent pathways[6].

While vitamin D deficiency may have played a contributing role in our patient, it is rarely implicated in causing proximal tubulopathy[2, 7, 8]. Our patient's initial serum calcium/phosphate levels were normal and her electrolytes started to normalize without continuous replacement, by the time of oral colecalciferol commencement. Although there have been no reports of IPD occurring in association with renal tubulopathy, we report a possible association with vitamin D deficiency, through exclusion of other causes. We postulate that direct infection by *S. pneumoniae* in the proximal tubules, resulting in tubular injury, could have occurred in our patient.

CONCLUSION

With this case, we highlight the interesting clinical phenomena of a patient with IPD who developed multiple electrolyte derangements likely secondary to Fanconi-like syndrome.

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