# Case report

# Rampant spread of infection in an afebrile immunecompetent patient presenting with young-onset ischaemic stroke

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#### SUMMARY

A 27-year-old healthy woman developed spontaneous right-sided orbital cellulitis, followed by left hemiparesis and cranial nerve palsies. MRI revealed underlying basal exudates and vasculitic infarction involving the pons and cerebellar peduncles, following which a cerebrospinal fluid examination confirmed acute bacterial meningitis. Although the patient remained afebrile, imaging revealed asymptomatic septic foci in bilateral lungs, empyema and pyelonephritis. Blood culture grew drug-resistant *Klebsiella pneumoniae*. The case highlights the absence of fever in an immune-competent patient presenting with young-onset stroke secondary to meningitis.

plantar reflex and Hoffman sign, were found on the left side. Cerebellar signs including abnormal finger nose finger test and heel-shin test on the right and gait ataxia with a tendency for rightward drift were present. Slow-beating gaze-evoked nystagmus on bilateral lateral gaze was noted. There were no signs of meningeal irritation.

## INVESTIGATIONS

Blood investigation performed at admission revealed neutrophilic leucocytosis  $(20.1 \times 10^9/L)$ , reference range:  $4-11 \times 10^9/L$ ) and mild thrombocytopenia  $(104 \times 10^9/L)$ , reference range:  $150-400 \times 10^9/L)$ , while the results of renal and liver function tests and urinalysis were unremarkable. Serum C reactive protein (53 mg/L, reference range: <6 mg/L)

## BACKGROUND

Acute meningitis can present with a combination of headache, fever, neck rigidity and focal deficits.<sup>1</sup> Orbital cellulitis is an infection of the loose areolar tissue around the eye that is drained by a system of veins with bidirectional valve-less communication with the intracranial vessels, allowing the potential spread to cerebrospinal fluid (CSF). We present a case of young-onset stroke that was caused by orbital cellulitis and subsequent meningitis spreading rapidly and extensively to multiple organs without a febrile response.

## CASE PRESENTATION

A 27-year-old woman, without prior comorbidities, presented with swelling and redness of the right eye and holocranial headache. The next day, she developed sudden onset left-sided hemiparesis and presented to our hospital after 12 hours of the onset of weakness. There was no history of fever, vomiting, blurring of vision, diplopia or prior history of recreational or medicinal drug use. On examination, she was afebrile with stable vitals, swollen right eyelid with warmth and erythema along with conjunctival suffusion without any pus discharge. Neurological examination revealed intact sensorium, right-sided lower motor neuron type of facial nerve palsy (House Brackmann grade IV, moderately severe dysfunction), left-sided hypoglossal nerve palsy with fasciculations and deviation to the left on protrusion, pronator drift present on the left side with power reduced to 4 (out of 5, Medical Research Council (MRC) scale) in the left half of body and associated mild sensory loss. Upper motor neuron signs, including extensor



**Figure 1** MRI brain. Postcontrast MRI (A–C) shows enhancement in the prepontine cistern (arrowhead, A), extending along the internal acoustic meatus (arrow, A). There is enhancement seen along the right cavernous sinus and the right optic canal (arrow, (B)), abscesses in the retrobulbar space, with preseptal thickening and enhancement. (Arrowhead, (B)) There is similar enhancement of the VII and VIII nerve complex. (Arrow, (C)) Also seen are the diffusion-weighted image (D) showing diffusion restriction in the right pons, middle cerebellar peduncle and paraventricular cerebellar cortex (arrowhead).

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and procalcitonin (1.3 ng/mL, reference range: <0.1 ng/mL) levels were markedly elevated.

A contrast-enhanced CT (CECT) of the head was performed initially, that did not reveal any prominent intracranial pathology and ruled out paranasal sinus involvement and otitis media. MRI brain performed with stroke protocol, at 20 hours of weakness onset, showed T2 and Fluid attenuated inversion recovery sequence (FLAIR) hyperintense signal in the prepontine cistern extending to the right internal acoustic meatus with contrast enhancement (figure 1A), as well as the right cavernous sinus and optic canal (figure 1B). Facial neuritis was evident at the internal acoustic meatus (figure 1C). Areas of restricted diffusion were seen in the pons and right cerebellar peduncle suggestive of infarcts (figure 1D). CSF examination was performed on the third day of admission, prompted by the imaging findings, revealed normal opening pressure with cytological and biochemical features of partially treated acute bacterial meningitis (total leucocyte count:  $0.1 \times 10^9$ /L with 80% polymorphonuclear cells (reference range: leucocytes up to  $0.005 \times 10^9$ /L, if all lymphocytes), RCCs: 60/mm<sup>3</sup>, protein: 150 mg/dL (reference range: 20-50 mg/dL), glucose: 30 mg/dL (corresponding blood sugar 109 mg/dL, reference range: 60% of blood sugar or >65 mg / dL)). GeneXpert and adenosine deaminase levels (7 IU/mL; reference range: positive if >10 IU/mL) for tubercular meningitis, cryptococcal antigen, and Herpex simplex virus PCR were negative, and bacterial culture was sterile. Blood culture grew Klebsiella pneumonia with susceptibility only to Imipenem and Colistin, and resistance to amikacin, cephalosporins, meropenem, piperacillin-tazobactam, and ciprofloxacin.

She was evaluated for the possible origin of the orbital cellulitis and meningitis. Chest radiograph showed pleural-based opacities in the right hemithorax. Subsequent CECT showed multiple pleural-based areas of consolidation, few of which showed central necrosis and feeding vessel sign with moderate right empyema (figure 2). A note was also made of bulky kidneys with wedge-shaped hypodense lesions. The findings were suggestive of septic emboli causing pulmonary and renal infarcts. Twodimensional transthoracic echocardiography did not reveal any vegetations or any other cardioembolic source.

#### **DIFFERENTIAL DIAGNOSIS**

We evaluated the cause of her lack of febrile response to disseminated infection and ruled out common acquired causes, including HIV infection, malnutrition, poorly controlled diabetes mellitus, steroid or other immunosuppressant therapy, haematological malignancy, chronic kidney disease and cirrhosis. After the resolution of the infection, primary immunodeficiency was evaluated and ruled out (table 1).



**Figure 2** Contrast-enhanced CT scan: lung window (A) shows peripheral lung nodule in right middle lobe, with central cavitation (arrow) and feeding vessel. The mediastinal window (B) shows right-sided pleural effusion (marked with an asterix) with pleural enhancement suggestive of an empyema.

Table 1 Primary immunodeficiency workup			
Investigation	Subtype	At 6 months follow-up	Reference ranges
T cell	CD3+ (%)	63.4	62–87
	CD3+CD4+ (%)	62.3	32–64
	CD3+CD8+ (%)	19.4	15–46
	CD4:CD8 ratio	3.2	0.69–4.2
B cell	CD19+ (%)	6.4	6–23
Natural Killer (NK) cell	CD3- CD16+CD56+ (%)	4.17	4–26
Dihydrorhodamine test	Unstimulated (MFI)	3.33	
(chronic granulomatous disease)	PMA stimulated (MFI)	1102	
	Neutrophil oxidative index	367	>100
Total antibody titres	lgG (mg/dL)	1520	700–1600
	IgM (mg/dL)	271	40–230
	IgA (mg/dL)	214	70-400

Neutrophil oxidative index: ratio of mean fluorescence intensity of PMA stimulated and unstimulated neutrophils

.MFI, mean fluorescence intensity; PMA, phorbol myristate acetate.;

## TREATMENT

She was treated empirically with intravenous piperacillin–tazobactam and vancomycin within 2 hours of admission, because of cellulitis. She was initiated on early facial physiotherapy and gait therapy. Antibiotics were escalated to intravenous imipenem after obtaining blood culture and sensitivity pattern (mentioned above) on the fifth day of admission. She did not receive steroids, aspirin or anticoagulants.

#### OUTCOME AND FOLLOW-UP

She was discharged to home after 4 weeks of antibiotics. At 6 months follow-up, she had a near-complete resolution in neurological symptoms: left hemiparesis (improved to 5/5 MRC scale), cerebellar ataxia, right facial palsy (House Brackmann grade II, mild dysfunction), hypoglossal palsy (midline tongue protrusion and occasional fasciculations), and in the size of right eye swelling. She was able to resume work 2 weeks after discharge and able to carry out all required tasks.

#### DISCUSSION

Acute bacterial meningitis is a fulminant infection, the culprit of which is usually among Streptococcus pneumoniae, Neisseria meningitidis or Haemophilus influenzae. Spontaneous gramnegative bacterial meningitis (GNBM) caused by organisms other than H. influenzae is rare in adults, accounting for 9% of all cases, and among them, Klebsiella has been reported sparsely.<sup>2</sup> Bacterial pathogens most often reach the blood-brain barrier via the bloodstream,<sup>3</sup> and only rarely can it be attributed to contiguous spread by bidirectional intracranial veins or directly across thin skull bones. For the latter, cavities in communication with the external environment, such as paranasal sinuses and middle ear, are far more likely primary sources than the orbit. Orbital cellulitis can lead to meningitis,4 5 as can meningitis lead to orbital cellulitis,<sup>6</sup> which is attributable to the bidirectional valve less cavernous sinus system. In our case, we propose the contiguous spread of infection from the orbital cavity to meninges and further bacteremia seeding the lungs and kidneys; alternatively, hematogenous spread from the orbit to meninges, kidneys and lungs.

In decreasing order of importance, the significantly low sugar levels, neutrophil predominance and mildly increased protein concentrations in the CSF suggest the diagnosis of bacterial meningitis instead of a parameningeal response to the orbital cellulitis or systemic inflammation.<sup>7</sup> Based on the blood culture growth of K. pneumonia and CSF analysis suggestive of acute bacterial process, it was attributed as the pathogen responsible for meningitis. A multicentre cohort study compared community-acquired meningitis due to K. pneumoniae and S. pneumoniae and found diabetes and cirrhosis to be risk factors in the former, along with a higher proportion of extrameningeal infections (41% vs 7%, p < 0.001) such as pneumonia, liver abscess, endophthalmitis and sepsis; the prevalence of focal neurological deficit was similar (18.5% vs 16.1%, p=0.76).<sup>8</sup> There was no difference in the CSF findings between the two groups. At the same time, blood investigations found Klebsiella meningitis to be more commonly associated with lower platelet counts or elevated creatine and bilirubin values, while S. pneumoniae meningitis had higher total leucocyte counts.<sup>8</sup> The antibiotic sensitivity pattern in our case was consistent with meropenem-resistant imipenem-sensitive, extended-spectrum beta-lactamase (ESBL) producing Klebsiella, which has been extensively studied and the differential carbapenem resistance attributed to selective efflux pumps.<sup>9</sup>

A previous case of hyper-mucoviscous Klebsiella meningitis presented with ischaemic stroke with infarcts in the cerebellar hemispheres, similar to our patient.<sup>10</sup> Both vasospasm and increased risk of thrombosis are implicated in the pathogenesis of ischaemic stroke in bacterial meningitis which can complicate as much as one in four patients with meningitis.<sup>11</sup> The internal carotid artery, during its course through the cavernous sinus, can be directly involved in the presence of septic thrombosis; this is more frequent with rhino-orbital mucormycosis.<sup>12</sup> Additionally, cranial nerves can be directly involved by inflammation and provide another mechanism of neurological deficits in meningitis patients, besides stroke and increased intracranial tension. The imaging findings in our case (figure 1C) are consistent with right facial neuritis and consequent lower motor neuron facial palsy.<sup>13</sup> A large study in patients of GNBM found a higher proportion of stroke, which was not statistically significant (30% vs 20%, p>0.05).<sup>2</sup> Tubercular meningitis is most often associated with small vessel infarcts in deep grey matter and brainstem due to its predilection for the basal meninges, and long-term corticosteroids are routinely prescribed to prevent neurodeficits and mortality while the role of aspirin is under investigation.<sup>14</sup> However, a similar benefit of these drugs has not been demonstrated in bacterial meningitis, except for a single dose of dexamethasone in pneumococcal meningitis. The patient was not considered for thrombolysis as she had crossed the window period in ischaemic stroke (4.5 hours).

The upper motor neuron type of involvement of long tracts (descending: right corticospinal tract and right spinocerebellar tract, and ascending: right dorsal column pathway) and lower motor neuron involvement of the facial nerve (right facial nerve) in the crossed fashion can be localised to the pons at the level of facial nerve nucleus; diffusion restriction was found on MRI at the level of right pons (figure 1D). Hypoglossal palsy with fasciculations suggests a lower motor neuron involvement and can be attributed to the basal meningeal involvement in the absence of imaging evidence of stroke at the level of medulla.

The present case had widespread septic embolism to the lungs and kidneys, which led to little or no symptoms (no chest or urinary complaints) or abnormal laboratory tests (no derangement of renal functions and bland urinanalysis). There are reported cases of immunocompromised patients lacking a febrile response to infections, possibly due to a decrease in cytokine response to bacterial antigens with a correspondingly low pyrogen synthesis.<sup>15</sup> Patients who fail to mount a febrile response during sepsis have an increased odds of death (33% vs 11%, p<0.01) as well as suppressed Human leukocyte antigen (HLA)-DR expression, a finding suggestive of monocyte dysfunction.<sup>16 17</sup>

To conclude, we present a case of rampant spread of infection from the soft tissue (right eye) to multiple organs (meninges, lung, pleura and kidney), caused by *K. pneumoniae*. The patient presented with predominant complaints of crossed hemiparesis, facial and hypoglossal nerve palsy as a result of ischaemic stroke and regional cranial nerve involvement. There were little or no manifestations of local inflammation or fever, even when there was radiological evidence for the pyogenic infections. We advocate that the absence of fever should not distract from diagnosing meningitis and that meningitis should be suspected as a cause of acute ischaemic stroke in young patients.

#### **Patient's perspective**

One day, I had noticed swelling over my right eye with redness, but since my vision was not affected, I paid no heed to it. I rushed to the hospital the very next day when I suddenly lost power in my left hands, legs, and my smile was awkward. I was shocked to found out that the cause of my stroke was an infection since I never had a fever during this period. Fortunately, with good supportive care and physiotherapy, I slowly regained function in my body and face, and I have returned to my college for further studies.

#### Learning points

- Fever may infrequently be absent in immune-competent patients despite disseminated infections with pyogenic organisms such as *Klebsiella*.
- Pyogenic meningitis usually results from haematogenous spread from the site of bacterial colonisation. In this process, multiple organs may be seeded by the bacteria simultaneously.
- Imaging findings suggestive of infection should prompt an urgent cerebrospinal fluid examination even in the absence of clinical signs of meningeal inflammation.

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## Unusual association of diseases/symptoms

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