CASE REPORT

QUAD fever: beware of non-infectious fever in high spinal cord injuries

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SUMMARY

A case of cervical spinal cord injury and quadriparesis with prolonged fever is being described. Initially, the patient received treatment for well-documented catheter-related bloodstream infection. High spiking fever returned and persisted with no obvious evidence of infection. The usual non-infectious causes too were carefully excluded. QUAD fever or fever due to spinal cord injury itself was considered. The pathogenetic basis of QUAD fever is unclear but could be attributed to autonomic dysfunction and temperature dysregulation. Awareness of this little known condition could help in avoiding unnecessary antimicrobial therapy and in more accurate prognostication. Unlike several previous reported cases that ended fatally, the present case ran a relatively benign course. The spectrum of presentations may therefore be broader than hitherto appreciated.

BACKGROUND

The reasons to submit this case report are three:

1. To inform clinicians of this potentially fatal complication of spinal cord injury.
2. To highlight the occurrence of fever attributable to the spinal cord injury itself so as to avoid injudicious antimicrobial therapy.
3. To stimulate interest into possible mechanisms of this poorly understood condition that could generate improved preventive or therapeutic options.

CASE PRESENTATION

A previously healthy male aged 46 years presented to the emergency room with a history of fall from a bike followed by inability to move both lower limbs and marked weakness in both upper limbs.

When seen 4–5 hours after injury, he was fully conscious and oriented with Glasgow Coma Scale (GCS) of 15/15. His vitals were stable with blood pressure 130/90 mm Hg, heart rate 98 beats per minute regular, respiratory rate 16 breaths per minute, oxygen saturation by pulse oximetry of 98% on room air and afebrile. Motor power in the proximal and distal muscles of the upper limbs was 3/5 and in the lower limbs was 0/5. Deep tendon reflexes were decreased in upper limbs and absent in lower limbs. Plantar reflexes were non-responsive bilaterally. His peripheral neurological examination confirmed quadriparesis with level of injury at C6 vertebral level and C7 spinal cord segmental level with loss of pin prick sensation and preservation of sweating below this level. His extent of spinal cord injury as described by American Spinal Injury Association Impairment Scale is C (ie, incomplete).

At the time of admission, complete blood count, blood sugar, kidney function and liver function parameters were within reference range. Focused abdominal sonography in trauma was negative.

After immobilising the neck with a hard collar and ensuring haemodynamic stabilisation, the patient underwent radiological evaluation. Chest X-ray and CT of the head were normal. MRI of cervical spine revealed severe injuries to the cord.

T2-weighted/Short-T1 inversion recovery images showed intramedullary cord hyperintensity extending from C5 to C7 causing cord expansion and cord oedema, posterior disc bulge at intervertebral discs at C2–C6 levels causing multilevel compression of nerve roots (figure 1).

The neurosurgical team opted for conservative management. No haemodynamic or ventilator support was required and the patient could be shifted out of acute care after 4 days. On the fifth day, he developed fever which was evaluated. He was diagnosed with hospital-acquired pneumonia, developed due to poor cough reflex, for which empirical antibiotic with cefoperazone and sulbactum were started. He was tracheostomised on day 6 in view of poor cough reflex and anticipated prolonged period of recovery. Two sets of blood cultures and tracheostomy secretions grew extended spectrum beta-lactamase producing *Escherichia coli*. The antibiotic therapy was changed to meropenem as per the culture and sensitivity report with prompt response to the fever. This pneumonia

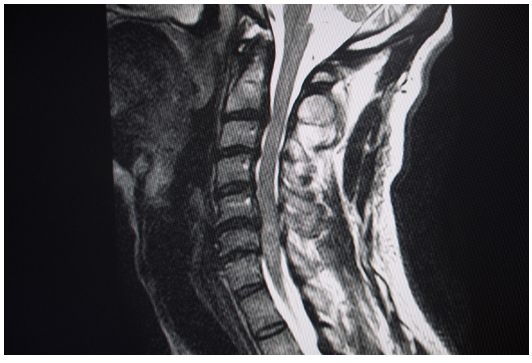

Figure 1 MRI cervical spine revealed severe injuries to the cord. T2-weighted/STIR images showing intramedullary cord hyperintensity extending from C5 to C7 causing cord expansion and cord oedema, posterior disc bulge at intervertebral discs at C2–C6 levels causing multilevel compression of nerve roots.

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Table 1 Serial investigations

Day of admission	White cell counts /µL	CRP	ESR	Procalcitonin
2	13 200			
3	22 000			
4	19 300			
5	10 400			
6	8500			
8	12 800			
10	14 200			
11	8600			
20	9000	7 mg/L (normal range 0–5)	55	0.21 ng/mL (normal range <0.5)
22	12 200			

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; TLC, total leucocyte count.

did not result in respiratory failure requiring mechanical ventilation support. After 1 week, on day 13 antibiotic was stopped with clearance of X-ray infiltrate. Patient remained afebrile for 2 days. On day 15, patient again developed fever. Keeping the possibility of drug-induced fever, on day 15 all drugs except Enoxiparin were stopped. Fever persisted despite stopping drugs for more than 72 hours, hence ruling out the possibility of drug-induced fever. For this new-onset fever again detailed investigations were done that included total leucocyte count (TLC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, blood cultures, urine examination and chest X ray. Serial TLC readings are depicted in table 1. CRP was 7 mg/L (normal range 0–5), ESR was 55, procalcitonin level was 0.4 ng/mL (normal range 0.15–2 ng/mL). Abdominal examination was found to be normal. An infection was excluded by the clearing of the infiltrate and blood and urine cultures returning sterile with other corroborative laboratory evidence such as normal TLC and procalcitonin levels. Trend of fever was remittent most of the time, responding partially to antipyretics touching the baseline occasionally. The maximum daily temperature trend is depicted in figure 2 and maximum pulse rate for the day is depicted in figure 3 for the duration of hospitalisation. There was no haemodynamic instability associated with this fever; however in the initial phase of the illness during the ICU stay, the patient transiently required vasopressors.

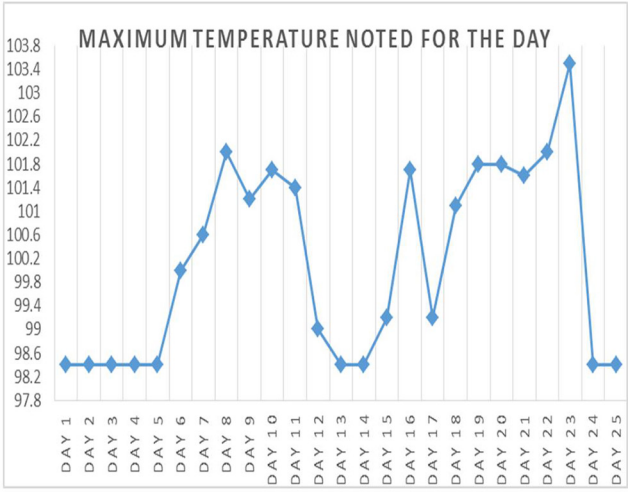

Figure 2 Maximum temperature noted for the day. X axis: days. Y axis: temperature in °Fahrenheit.

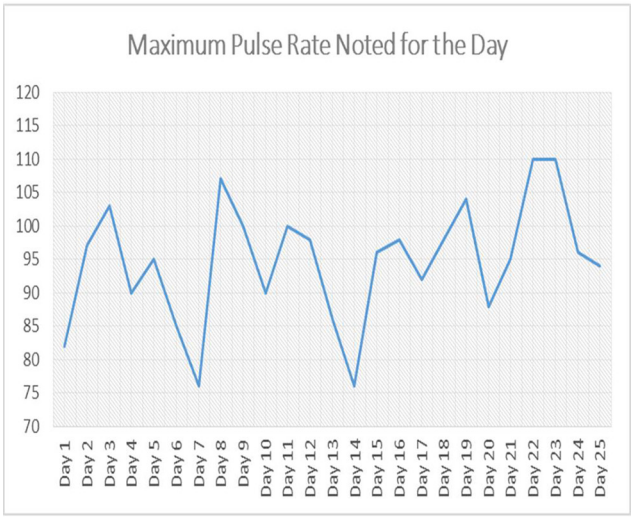

Figure 3 Maximum pulse rate noted for the day. X axis: days. Y axis: pulse rate per minute.

Patient had not received any neuroleptics, tricyclic antidepressants or selective serotonin reuptake inhibitors either before admission or throughout the hospital stay. To exclude drug-associated fever, all drugs except enoxaparin for deep vein thrombosis (DVT) prophylaxis were stopped. D dimer and thyroid function tests were normal, excluding the possibilities of venous thromboembolism and hyperthyroidism. There was no clinical evidence of any heterotropic ossification. Patient reported no pain over or around the joints. Also there was no swelling or decreased range of motion at the joint. Heterotropic ossification is generally reported to occur between 1 and 6 months postspinal injury with a peak incidence at 2 months. This patient was in the early stage of the injury with no clinical evidence in support of this diagnosis, so this possibility was also excluded.

A diagnosis of QUAD fever was made after excluding all infectious as well as other potential non-infectious causes of fever.

INVESTIGATIONS

TLC readings are depicted in table 1.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses were:

- Bloodstream infection
- Catheter-associated urinary tract infection
- Hospital-acquired pneumonia
- Drug fever
- Hyperthyroidism
- DVT
- Abdominal infections

TREATMENT

No specific treatment is required for this illness. Identifying the correct cause of fever and fever control with antipyretics are the standard of care.

OUTCOME AND FOLLOW-UP

Patient was discharged on 27th day after admission and was afebrile since 2 days prior to discharge.

DISCUSSION

This patient with cervical spinal cord injury (SCI) presented with unremitting fever, which is attributable to QUAD fever after having excluded the usual causes.

Autonomic dysfunctions are a common consequence of cervical and upper thoracic spinal cord injuries.[1] Autonomic dysfunction can manifest in many ways-neurogenic shock,bradycardia, orthostatic hypotension, dysreflexia, loss of sweating and temperature dysregulation[2] Although thermal regulation is described as one of the autonomic phenomena, the precise mechanism of this dysfunction is not known.[1 3 4] Fever in high SCI is hypothesised to be caused by disruption in various connecting pathways to hypothalamic temperature regulation centres.[3 4]

There are three categories of thermodysregulation.[2] First is poikilothermic or environmental fever which is the inability to regulate temperature in extreme environmental conditions. In hospital settings this entity is rare owing to controlled temperature conditions. The second is exercise-induced fever[5] and the third is the so-called QUAD fever, which is defined as a fever that cannot be attributed to an infectious or other non-infectious cause in patients with high SCI.[2 4] QUAD fever was first described in 1982 by Sugarman *et al*,[6] as an idiopathic extreme elevation of core temperature usually >101.5°F in patients with SCI. It is found to occur in the first several weeks of SCI and may remain for longer periods extending up to months.[7] It usually occurs in patients with quadriplegia but since it may also occur in high thoracic SCI with paraplegia, it is also referred to as SCI fever.[8]

Fever, infection or both occurred at some time during hospitalisation in 67% of patients in a referral SCI services.[6] The most common causes were urinary tract infection, soft tissue infections, decubitus ulcer and thromboembolic disease.[7] The incidence of fever of unknown origin (neurogenic fever) ranged from 2.6% to 27.8% with a mean incidence of 8.0% and a median incidence of 4.7%.[4]

QUAD fever may also be an early feature for the development of severe autonomic dysfunction.[8] It may present as malignant hyperpyrexia with multiorgan failure and shock.[8 9 10] In some cases of malignant hyperpyrexia, fever has been controlled with the help of various invasive and non-invasive cooling methods used for other malignant hyperthermic syndromes, although exact protocols to control temperature in this kind of fever is not described.[10] Early aggressive control of this malignant fever is extremely important to prevent mortality.[8 9 10]

By identifying this disorder, we can minimise unnecessary antimicrobial use and improve prognostication for the patient. The present case had high-grade fever without obvious infectious source. Procalcitonin has been found to be a reliable marker to exclude bacterial infection.[11] Other non-infectious causes of fever such as the neuroleptic malignant syndrome, serotonin syndrome and malignant hyperthermia and drug fever were excluded due to lack of their associations. DVT and hyperthyroidism were also excluded. Thus, QUAD fever was diagnosed by careful exclusion of infectious and other non-infectious causes.[12]

Clinicians should always consider the possibility of QUAD fever in cases of high SCI including cervical and upper thoracic spinal cord associated with fever, when other possible causes are reasonably excluded.[13] There are many established algorithms to manage neurogenic fever because of traumatic brain injury;[14] however, a clinical pathway and diagnostic algorithm to guide and evaluate cases of unremitting fever in SCI is lacking.[3 4] The mechanism, pathogenesis, impact on mortality, length of stay and neurological recovery in cases of QUAD fever are not well understood as number of cases reported are few and further studies are needed to elucidate this disorder.[4]

Learning points

- QUAD fever, a non-infectious complication, should be considered in the evaluation of fever in spinal cord injury.
- Although malignant forms of QUAD fever have been described, benign presentations should also be recognised.

Contributors JG was involved in all stages of manuscript preparation and online submission of the paper. RJ was involved in literature search and collecting radiology films. PB was involved in collection of data. RKM was involved editing of the draft and final preparation of case reports.

Competing interests None declared.

Patient consent Obtained from next of kin.

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Reminder of important clinical lesson