Case Report

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Heterotopic ossification Post-Guillain–Barre syndrome in Saudi Arabia: a case report

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Background: Heterotopic ossification (HO) is the formation of bone within the soft tissues. It can be a complication of Guillain–Barre syndrome (GBS). There are many risk factors for HO, including male sex, mechanical ventilation, and neurogenic trauma. Myelin and axons are the main targets and areas of injury in GBS, an autoimmune-inflammatory neuropathy. Literature shows that this may possibly be associated with the initial administration of the COVID-19 vaccine and GBS.

Presentation of the case: A 27-year-old male was diagnosed with bile reflux gastritis. Days later, he presented to the emergency room (ER) with progressive weakness and a critical condition that required ICU. The patient undergoes intubation and remains in the ICU for 4 months. The patient, after extensive rehabilitation, started to complain of left hip pain and limitations of motion. Radiographs confirmed the HO diagnosis. Past drug history showed patients received a single dose of the COVID-19 vaccine 15 days before presentation to the ER.

Discussion: There is no clear association between the COVID-19 vaccination and GBS. HO is the formation of abnormal bone within soft tissue. HO post-GBS usually affects large joints like the hips, knees, and shoulders. Researchers poorly understand the pathogenesis of GBS.

Conclusion: Despite the absence of a definitive correlation between GSB and the COVID-19 vaccine. Physicians should maintain a state of suspicion while treating patients with a progressive weakness. Additional research is required.

Keywords: arthroplasty, case report, COVID-19, Guillain–Barré syndrome, heterotopic ossification

Introduction and background

Heterotopic ossification (HO) is defined by the abnormal formation of new lamellar bone within the extraskeletal structure[1]. Neurogenic heterotopic ossification (NHO) is the same by definition and related to a neurological disorder, which is a complication of Guillain–Barre syndrome (GBS)[2]. Zelilig *et al*.[1] conducted a long-term prospective study on the neurologic and functional outcomes of GBS patients admitted for rehabilitation for 3 years, and the result was that four (6%) out of 65 patients had HO. Several risk factors include male sex, genetic susceptibility, neurologic trauma or injury, tissue hypoxia, spasticity, extended coma, mechanical ventilation, and fever lasting more than 5 days[1,2]. The diagnosis of NHO is usually not apparent in the initial phase and sometimes requires a bone scan to confirm the diagnosis[1]. In our care, the diagnosis was missed for several months until the patient started complaining of pain and later loss of motion in the left hip. GBS is an autoimmune-inflammatory neuropathy that primarily targets and damages the myelin and axons[3]. It's usually after infectious diseases and can range from weakness, which is progressive ascending, to complete paralysis with a flaccid muscular tone[1]. A review article by Miao *et al*.[4] aimed to conduct a retrospective analysis of instances of GBS that have been recorded after COVID-19 immunization, and they concluded the study with that there may be an association with the first dose of vaccine, especially DNA vaccines. To the best of our knowledge, this is the first case in Saudi Arabia in the literatures that reports HO post-GBS. This case report has been reported in line with the surgical case report (SCARE) guidelines[5].

HIGHLIGHTS

- A 27-year-old male was diagnosed with bile reflux gastritis.
- Three days later, patients start to have progressive dizziness and generalized fatigue.
- Two weeks later, the patient diagnosed with Guillain–Barre syndrome.
- The patient shifted to the intensive care unit, was intubated for 4 months, and later started to have left hip pain and limitations of movement. Plain radiographs show heterotopic ossification.
- Past drug history shows patients received a single dose of COVID-19 immunization 15 days before symptoms started.

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Patient information

A 27-year-old male was presented to our outpatient department (OPD) with left hip limitation of movements. 3 years ago, he went to emergency room (ER) by ambulance on 17 June 2021, with recent progressive dizziness and generalized fatigue. The patient was then discharged from the hospital after some investigations. The patient is single, a nonsmoker, and fully dependent on himself; past psychosocial history and genetic information in his family were irrelevant. There is no history of head trauma, traumatic brain injury, or spinal cord injury. The patient's weight was 90 kg, his height was 189 cm, and his BMI was 25.20. The patient's past drug history indicated that he received one COVID-19 vaccination (AstraZeneca) 15 days before presentation to the ER. Three days after vaccination, the patient started to have abdominal pain and recurrent vomiting. The doctors at the local hospital diagnosed him with a gastric ulcer and prescribed antibiotics and antacids, but there was no noticeable improvement. On 13 June 2021, the patient went for an upper gastrointestinal endoscopy, and the results showed an esophagus with a normal mucosa-Z-line at 38 cm from the oral incisor, hiatus hernia (Hells grade I), a stomach with excessive biliary secretion and antral erythematous hyperemic mucosa suspected of biliary gastritis, duodenum was unremarkable, and the final diagnosis of upper gastrointestinal endoscopy was bile reflux gastritis. After three weeks of the first ER visit, the patient presented with severe progressive dizziness, generalized fatigability, and severe bilateral lower leg weakness. The lower limps' power was 0/5, and the upper limps' power was 3/5. Cerebrospinal fluid (CSF) analysis through lumber puncture showed normal cells count, protein 54 mg/dl (normal 15–45), and glucose 70.2 mg/dl (normal 50–80). Random blood sugar 8.1 mmol/l (normal 3.9–7.8). Creatine phosphokinase 444 U/l (normal 39–308). Direct bilirubin 5.3 umol/l (normal 0–4.5). Other lab investigations were unremarkable. MRI of the brain and spine, computed tomography (CT) of the brain, and chest CT angiogram were unremarkable. Electromyography (EMG) showed a severe form of axonal injury. The patient was critically unstable, looked ill, and had a Glasgow coma scale (GCS) of 13/15 with tachypnea and dyspnea. The patient then shifted to the ICU and was given methylprednisolone, three doses of intravenous immunoglobulin (IVIG), and seven sessions of plasmapheresis. A sedative was started, a tracheostomy was done, and intubation performed. The medical team diagnosed GBS as the final diagnosis. The patient was intubated in the ICU for about 4 months, then extubated and started rehabilitation. Nine months after extubation, the patient started to have left hip pain and restricted range of motion, which was progressive. Three years after the onset of GBS, a plain radiograph (Fig. 1) and CT scan (Fig. 2) show HO. The patient continued with rehabilitation, went back to the gym, kept motivated all the time, and we will follow-up every 6 months.

Discussion

GBS is often preceded by infectious diseases or other immune stimuli that lead to an abnormal autoimmune reaction that' targets nerves. Mimicking molecularity between microbes and nerve antigens is the primary cause of GBS, at least in *Campylobacter jejuni* infection. After immunity stimulation for 1–2 weeks, in the acute phase, the limb weakness is often associated with sensory and cranial nerve involvement until they reach maximum weakness within 2–4 weeks. Sixty-six percent of adult patients have signs of a respiratory or gastrointestinal tract infection before developing weakness within 4 weeks[6]. There are many types of GBS with different pathogenies, but autoimmune attacks to peripheral nervous system (PNS) is consistent[7]. To date, there is no clear evidence confirming the relationship between GBS and COVID-19 vaccination[4,8,9]. The link between vaccination and the higher incidence of GBS has only been established for the influenza vaccine, resulting in 1–2 instances of GBS per 1 million doses of the influenza vaccine[4]. Keddie *et al*.[10], study showed no association between COVID-19 immunization and GBS. Sadoff *et al*.[11], trial showed no differences in GBS rate between COVID-19 vaccination, and placebo, making the relationship might be just theoretical rather than causal.

However, there has been many reported cases of GBS post-COVID vaccination. Wan *et al*.[9], reported three cases of GBS post AstraZeneca vaccination. Tabatabaee *et al*.[12], reported 3 cases post AstraZeneca and Sinopharm vaccinations. Khan *et al*.[7], mentioned 5 cases of GBS post-COVID-19 vaccination. Sriwastava *et al*.[13], conducted a review of case reports and series regards COVID-19 vaccination and neurological manifestations. The study includes total 51 patients, in which GBS is the most PNS findings, and higher after the first dose of AstraZeneca vaccine in 64% of 51 patients. World Health Organization (WHO) report indicated that increasing cases of GBS only observed in adenoviral vector-based vaccines (AstraZeneca and Janssen), but not with mRNA-COVID-19 vaccines (Moderna and Pfizer-BioNTech)[14].

One of causes of GBS post-COVID-19 vaccination might be a molecular mimicry mechanism due to viral vector vaccine and immune system reaction, which might trigger GBS[15]. Given that the SARS-CoV-2 spike protein can bind to cell surface sialic acids, including those on the angiotensin-converting enzyme (ACE)2 receptor, one theoretical explanation for the COVID-19 vaccines could involve a cross-reaction between antibodies produced to the spike protein and the sialic acid-containing glycoproteins[16,17]. Hematogenous spreads for COVID-19 might be responsible of central and peripheral neuron invasion, which untimely might cause different neurological conditions, including GBS[18].

HO is a pathological condition that refers to the aberrant development and buildup of bone in tissues that are not typically osseous. The exact pathogenesis of HO is still unclear, and various mechanisms have been proposed, but none possess complete scientific coherence[1]. It commonly develops in the hip, knee, and shoulder joints, leading to pain and restricted joint mobility[2]. COVID-19 infection can be associated with HO. Meyer *et al*.[19], reported 4 cases of HO post-COVID-19, in which all of them needed mechanical ventilation. Ploegmakers *et al*.[20], reported 2 cases of HO post-COVID-19, in which both needed mechanical ventilation. The exact etiology casing HO post-COVID-19 in unknown; however, there are many factors that may cause HO to appear post-COVID-19 infection, like immobilization, mechanical ventilation, and inflammation[21]. There are considerable changes in genetic expression patterns across cells in bone fragments from patients with normal and heterotopic bone. Overexpression of osteocalcin mRNA in HO-isolated cells accompanied with a large up-regulation of type I collagen could relate to high activity of the heterotopic bone. Local inflammation may affect soft tissue mesenchymal stem cells, which release prostaglandins ending with ossification and new bone formation[22]. Other explanation suggests that bone trauma causes the release of bone morphogenic protein (BMP), the

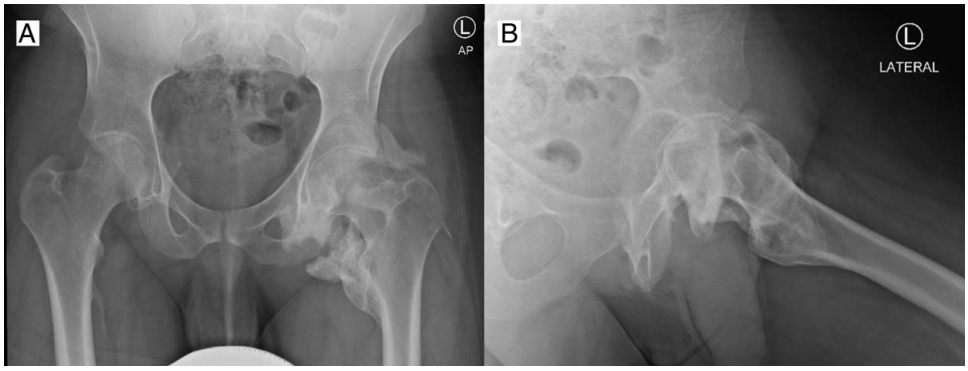

Figure 1. Plain radiographs of the pelvis AP (A) and frog leg lateral (B) shows heterotopic ossification.

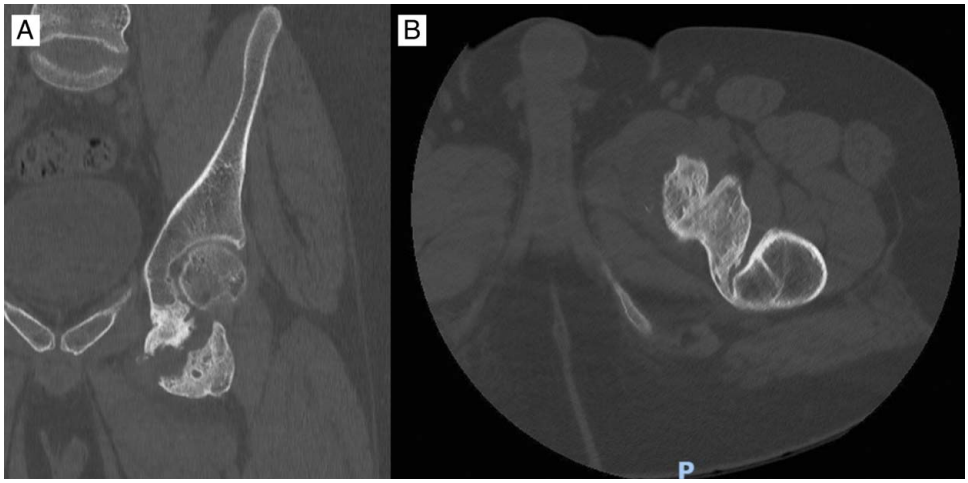

Figure 2. Computed tomography scan of the left hip coronal (A) and axial views (B) shows heterotopic ossification.

opening of blood-nerve barrier (BNB), and induce neuroinflammation. After opening BNB, the neural crest stem cells located in endoneurium are exposed to BMP, and inflammatory medicated cytokines ultimately released into blood circulation. Elevated BMP will enhance the formation of brown adipose tissue (BAT), promoting hypoxia and angiogenesis[2,23,24]. The neurogenic insult induces neuroinflammation cascade, increased BMPs, and BAT synthesis will promote the osteogenic mesenchymal cells differentiation into osteoblasts and chondrocytes towards NHO[2,7].

There was no head trauma in our patient[25], and as the exact causes of GBS were poorly understood, we could not rule out other causes of the condition. This case report had some limitations, we retrospectively reviewed our patient after he presented to our OPD 3 years after the onset of GBS, and the initial treatment was in another facility. The diagnosis was missed initially, so no full investigation of the acute phase of the disease was available. Later, when the patient complained of a left hip, it was too late to investigate a 3-phase bone scan or alkaline phosphates[26]. Examination and plain radiographs diagnosed HO.

Conclusion

Although no clear association between GBS, COVID-19 infection, and COVID-19 vaccination, physicians must exercise high suspicion in patients with progressive weakness after COVID-19 infection or vaccination. Further levels 1 and 2 studies needed to confirm or deny this association.

Ethical approval

The case report does not require ethical approval from the institution from which it originates.

Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of the journal.

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Author contribution

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