Case Report

Guillain–Barré syndrome as a fatal complication of SARS-CoV-2 infection – An autopsy case

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ABSTRACT

We presented a case of a 57-year-old female, who was tested positive for SARS-CoV-2 infection and was admitted to a hospital seven days later with signs of early pneumonia. The second day after her admission to the hospital, and nine days after the first positive PCR test, examination showed progressive ascendant weakness of the arms and legs with persisting paresthesia, lab tests showed increased concentration of proteins in the cerebrospinal fluid with albumino-cytological dissociation. She was diagnosed with Guillain-Barré syndrome (GBS). She was on low-flow oxygen support of 3 L/min, with good oxygen saturation (97–99%), without clinical or radiological progression of pneumonia. After receiving a negative PCR test for COVID-19 (11 days after the initial, positive test), four days after admission, she was set to be transferred to a specialized neurology clinic, however, she died unexpectedly during admission. The autopsy showed light to moderate lung edema, signs of moderate to severe coronary atherosclerosis and early myocardial ischemia. Histochemical and immunohistochemical staining of the peripheral nerves sampled from the cervical and brachial plexuses, showed foci of demyelination as well as infiltration with inflammatory cells, predominantly macrophages, and lymphocytes to a lesser degree. It was concluded that the causes of death were a breathing disorder and the paralysis of the diaphragm due to inflammatory polyneuropathy caused by GBS, initiated by SARS-CoV-2 infection. With the lack of similar autopsy cases, we believe that the presented case could be a valuable addition to the understanding of GBS development in SARS-CoV-2 related cases.

1. Introduction

Guillain–Barré syndrome (GBS) is an inflammatory polyneuropathy characterized by an acute onset, rapid progression, symmetric muscle weakness, unstable ambulation, and hypo- or areflexia. At the time of onset, the weakness is predominantly distal, with weakness in the legs spreading ascending, to the upper limbs and the face, and with the complete loss of deep tendon reflexes [1].

GBS has various phenotypes including the classic immune-mediated acute-onset demyelinating polyradiculoneuropathy (acute inflammatory demyelinating polyneuropathy—AIDP) typically presenting with ascending weakness, loss of deep tendon reflexes, and sensory deficits. Diagnosis of GBS relies on the results of clinical, electrophysiological, and cerebrospinal fluid (CSF) examinations (classic albuminocytological dissociation). Based on electrophysiological features, the three main subtypes include: AIDP, acute motor axonal neuropathy (AMAN), and acute motor sensory axonal neuropathy (AMSAN) [1,2].

GBS commonly appears within a couple of weeks after respiratory or gastrointestinal infection. The most common infections are those including bacteria – Campylobacter jejuni, Mycoplasma pneumonia, Haemophilus influenza; or viruses – cytomegalovirus, Epstein–Barr virus, measles, influenza A virus, Hepatitis E virus, enterovirus D68, and Zika virus as well as other Corona viruses [1,3–5]; some cases are related to other immune stimuli that induce an aberrant autoimmune response targeting peripheral nerves and their spinal roots. Pathogenesis of GBS includes a post-infectious mechanism, with molecular mimicry and antibody cross-response. Other mechanisms may be present in GBS associated with a Zika virus infection, which has earlier onset and associated antiganglioside antibodies are rarely present, suggesting a parainfectious pathogenetic mechanism [5].

Typical clinical presentation of classic GBS includes pain, paresthesia, numbness, and rapidly progressive bilateral limb weakness that usually starts in the distal lower extremities and progresses upwards over a period of hours or days, until the arms and facial muscles also

become affected, leading to bulbar weakness and respiratory difficulties. The weakness reaches its peak 2–4 weeks after symptom onset [1].

Since the start of the Covid-19 pandemic, GBS has also been associated with COVID-19 infection [2,6–15]. We presented one such case with a fatal outcome.

2. Case presentation

In June 2020, after having light malaise and diarrhea, a 57-year-old female was tested positive for SARS-CoV-2 infection. She had no significant risk factors or associated diseases and initially had a mild clinical picture, with a normal chest X-ray and normal laboratory findings, so she was sent home. She did not measure her body temperature while she was at home. Four days later, she started coughing and felt malaise, severe fatigue, paresthesia (tingling) in her arms and legs, and weakness in her legs. After she addressed her doctor, she was immediately admitted to a hospital (seven days after her first positive test). Her X-ray showed signs of early interstitial pneumonia with oxygen saturation of 98%, while laboratory findings showed slightly elevated LDH (637 U/l, normally < 241 U/L) and CRP (11.6 mg/L, normally < 5 mg/l), as well as D dimer (1.52 ng/mL, normally < 0.5 ng/mL). The second day after her admission to the hospital, and nine days after the first positive PCR test, examination showed progressive ascendant weakness of the arms and legs with persisting paresthesia, while the patient was unable to walk. Additional neurological examination also showed light dysarthria, light weakness of the tongue, neck anteflexion muscles, moderate flaccid paraparesis of arms, flaccid paraplegia of legs with minimum response of leg reflexes, lower sensibility below the level of twelfth thoracic vertebral nerves and sphincter incontinence. A CT scan showed old ischemic microchanges, without acute pathological findings. Lumbar puncture showed increased concentration of proteins in the cerebrospinal fluid with albumino-cytological dissociation (proteinorrachia) – 1.11 g/L (normally up to 0.4 g/L). Analyses on anti-gangliosides antibodies were not performed. Based on the clinical presentation, the patient was diagnosed with Guillain-Barré syndrome. She was treated with symptomatic therapy, antibiotic and antiviral therapy, prophylactic doses of low-molecular-weight heparin, rehydration therapy and oxygen support for four days in total. She was on low-flow oxygen support of 3 L/min, with good oxygen saturation (97–99%), and there was no clinical or radiological progression of pneumonia. After receiving a negative PCR test for COVID-19 (11 days after the initial, positive test), four days after admission, she was scheduled for intravenous immunoglobulin therapy (as the initial treatment for GBS) and set to be transferred to a specialized neurology clinic. However, during admission to the neurology clinic, she died unexpectedly.

The autopsy was performed five days later. The body was 167 cm in length and 64 kg in weight (BMI 23.0 kg/m^2). The gross autopsy finding included light brain edema, light to moderate lung edema (total weight 1210 g), signs of moderate to severe coronary atherosclerosis, and suspected acute ischemic lesion of the myocardium. Microscopic examination of the heart showed moderate atherosclerosis, early ischemic changes on the myocardium (interstitial edema, focal leucostasis without inflammatory infiltration, focal fragmentation and attenuation of myocardial fibers, focal contraction band necroses) as well as focal fibrosis, while there were no signs of myocarditis. There were neither macroscopic, nor microscopic signs of pulmonary thromboembolism. A microscopic examination of the lungs showed only light focal alveolar edema and foci of fresh alveolar bleeding, focal infiltration of lung interstitium with lymphocytes and macrophages as well as foci of linear fibrosis. Microscopic findings on other internal organs were insignificant. We also examined the peripheral nerves sampled from the cervical and brachial plexuses with regular (hematoxylin-eosin) and special/histochemical (Luxol Fast Blue) staining as well as immunohistochemical staining (LCA, CD68, and CD3 staining) (Figs. 1 and 2). These nerves were sampled since they give rise to the phrenic nerve, which originates mainly from the fourth but also from the third and fifth cervical nerve.
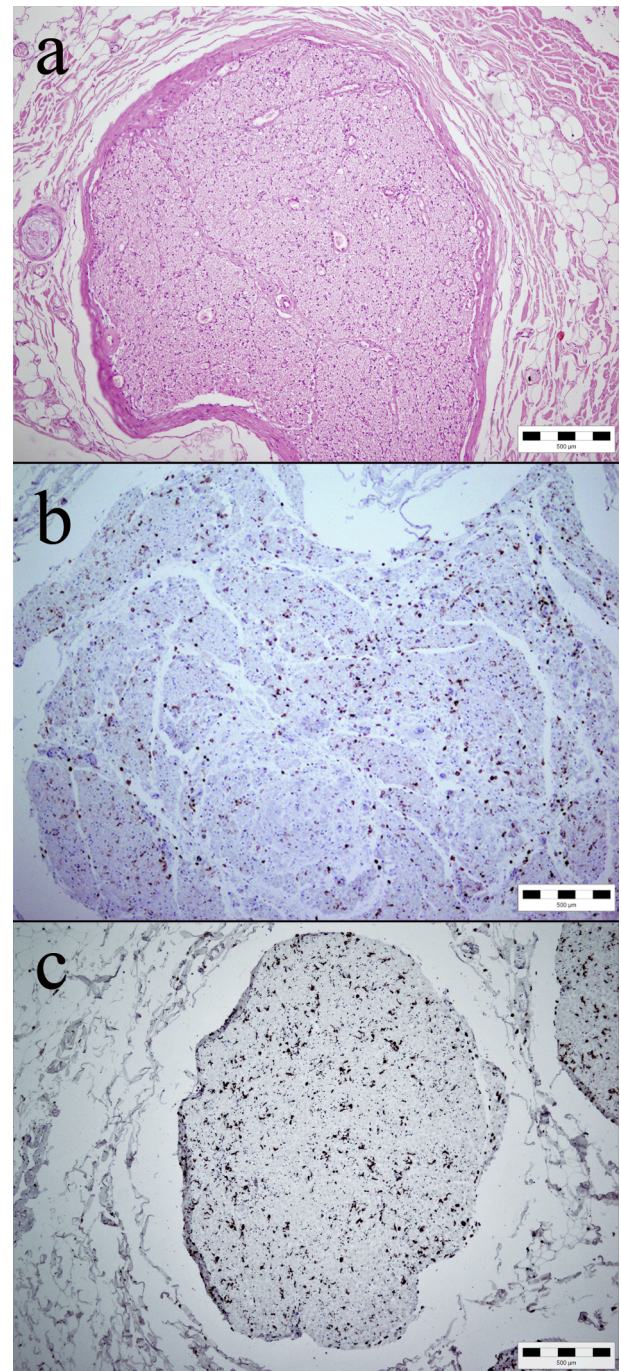

Fig. 1. Peripheral nerve from brachial plexus with inflammatory infiltration; **a** H/E stain (x100); **b** LCA immunohistochemical staining showing lymphocytic inflammatory infiltrate (x100), while CD68 stain (**c**) shows the predominance of macrophages (x100).

The phrenic nerve provides primary motor and sensory innervation of the diaphragm. Histological examination of these nerves showed foci of demyelination as well as infiltration with inflammatory cells, predominantly macrophages, and T lymphocytes (CD3 +) to a lesser degree. With the absence of significant pneumonia, diffuse alveolar injury, pulmonary thromboembolism, other types of thrombosis, myocarditis or other clinical and autopsy signs associated with COVID-19 on the one hand [16], and the presence of both clinical and autopsy signs related to Guillain-Barré syndrome (demyelination and inflammation of peripheral nerves giving rise to the phrenic nerve) on the other, it was concluded that the causes of death were a breathing disorder and the
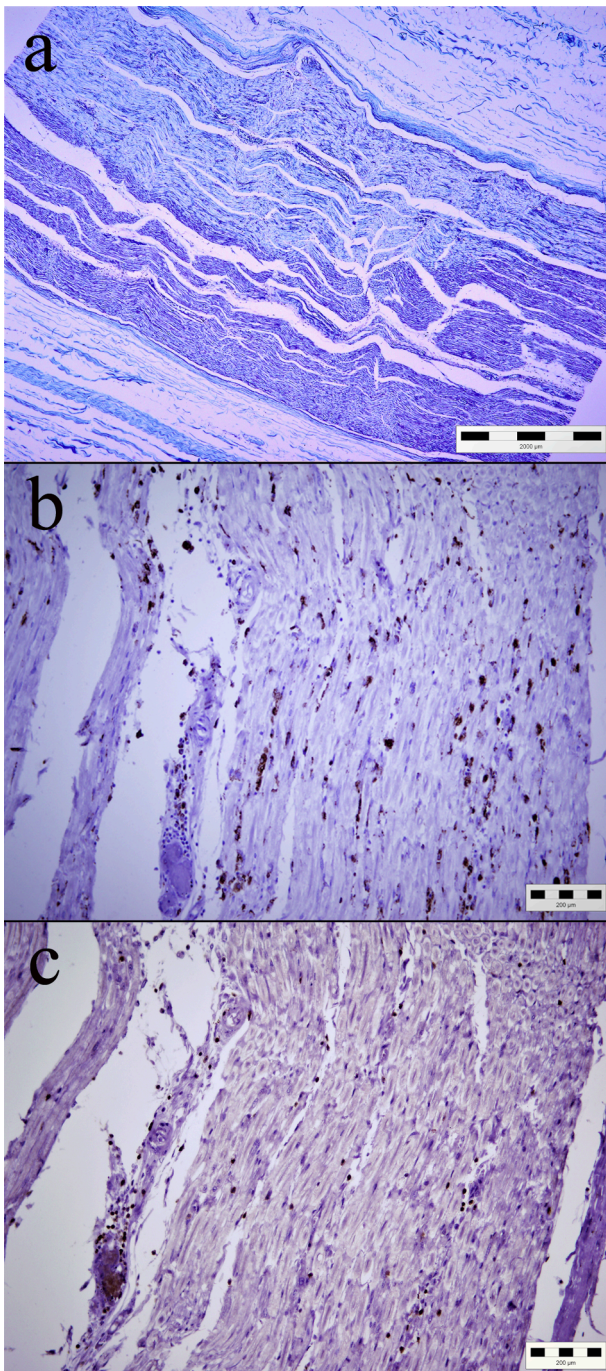
Fig. 2. a A peripheral nerve from brachial plexus stained with Luxol-fast blue shows brighter demyelination foci (x4). Immunohistochemical staining also shows nerve infiltration with CD68 positive macrophages (x200) (**b**), and to a lesser extent, CD3 positive T lymphocytes (x200) (**c**).

paralysis of the diaphragm due to inflammatory polyneuropathy caused by Guillain-Barré syndrome, initiated by SARS-CoV-2 infection.

3. Discussion

Guillain-Barré syndrome may be a life-threatening disorder with frequent morbidities, even with the best treatment available. In general, mortality rates in Europe and North America vary between 3% and 7% [1,3]. The most common causes of death include ventilatory insufficiency or pulmonary complications in the acute progressive stage or autonomic dysfunction, including arrhythmia. Death may occur even in later stages, after discharge from an ICU to a general neurology ward [3]. The pathogenetic mechanism is not clear, and there is contradictory information on whether GBS associated with COVID-19 has the characteristics of a post-infectious mechanism, with molecular mimicry and antibody cross-response, or perhaps more probably, a parainfectious pathogenetic process [5].

A systematic review by Palaiodimou et al. [4] identified the pooled GBSs prevalence amongst COVID-19 patients of 0.15‰, without any relevant data regarding mortality. The systematic review by Freire et al. [5] identified six fatal outcomes out of 105 cases (5.7%); Aladawi et al. [6] identified six fatal cases out of 109 (5.5%); Zuberbühler et al. [7] identified two out of 48 cases (4.2%), while Abu-Rumeileh et al. [2] identified four fatal cases out of 68 (5.8%). Regardless of the fact that all of these systematic reviews are based on a relatively small number of cases, it seems that the percentage of fatal outcomes is within range for GBS that is not COVID-19 related. These systematic reviews showed male predominance (65–68.5%), the average age of 55–57 years, with a wide age range (11–99 years) [2,5–7].

Through the literature search and the above-mentioned systematic reviews, we identified eight case reports of fatal COVID-19 related GBS patients with a fatal outcome [8–15]. In all of these cases COVID-19 infection was confirmed with PCR tests, and all of them had clinical signs of GBS. There were five males and three females, with the age range between 55 and 76 years, and the duration of hospital treatment from 1 to 32 days. In all eight cases, death occurred due to progressive respiratory failure. No autopsy was performed in any of them.

In our presented case, the cause of death was not directly related to COVID-19. There were no signs typically associated with COVID-19, such as diffuse alveolar injury, significant pneumonia, pulmonary thromboembolism, thrombosis in general, myocarditis, or other [16]. However, the cause of death was undoubtedly related to GBS caused by a SARS-CoV-2 infection. We histologically demonstrated inflammation and demyelination of the peripheral nerves sampled from the cervical and brachial plexuses (Figs. 1 and 2), which give rise to the phrenic nerve. The fact that the phrenic nerve provides the major innervation for the diaphragm could explain the breathing disorder in the context of GBS, and it could also explain the histological finding of pulmonary edema. Our findings – immunohistological staining strongly positive for CD68, with just occasional positivity for CD3 antibodies, show the predominance of macrophages over lymphocytes and also suggest the predominance of humoral over the cellular autoimmune response in this case. We also cannot exclude the possibility of autonomic dysfunction with heart damage caused by GBS, especially taking into account microscopic signs of early myocardial injury in the presence of moderate to severe coronary atherosclerosis.

In addition to the clinical signs that were present, we also demonstrated autopsy signs of GBS and related GBS directly to the fatal outcome in the presented case by showing inflammation and demyelination of the peripheral nerves, which might have caused paralysis of the diaphragm and cessation of breathing. In our literature search, we did not find similar autopsy cases. Taking into account the fact that death was unexpected – during the patient's transfer to the neurology clinic, without previous satisfactory oxygen saturation, the conclusion that the cause of death was GBS becomes even more probable. It makes this case different from the others previously published. With the lack of similar autopsy cases, we believe that the presented case could be a valuable addition to the understanding of GBS development in SARS-CoV-2 related cases.

4. Declarations

participants or animals performed by any of the authors.

Consent to participate: This study was the result of a routine forensic autopsy and did not compromise any procedure; therefore, obtaining formal consent was not necessary.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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