Acute incidence of Inflammatory bowel disease and Guillain-Barré syndrome following COVID-19 vaccination

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Abstract

Background: Since 2019, the Covid-19 pandemic has led to the manufacturing of a wide range of different types of vaccines with different mechanisms of action. The data collected from various studies indicate that complications such as injection site pain, headache, fatigue, fever, and malaise are the most common side effects of Covid-19 vaccination. The most common site-specific complications in the gastrointestinal tract and nervous system in different studies were diarrhea, abdominal pain, nausea, vomiting, dizziness, headache, myalgia, peripheral neuropathy, and demyelinating diseases, respectively. In this study, we report a case that developed complications such as Guillain-Barré syndrome and Crohn's colitis following Sinopharm/BBIBP COVID-19 vaccination. The course of Crohn's disease (CD) was also complicated by CMV, and the patient developed fulminant colitis, which led to peritonitis.

Case presentation: The patient was a 36-year-old Caucasian male who presented with severe generalized abdominal pain, nausea, vomiting, fever, dyspnea, and fatigue 4 days prior to admission. He mentioned a recent hospitalization due to bilateral ascending paraparesis, which was diagnosed as Guillain-Barré syndrome and treated with intravenous immunoglobulin. He also complained of watery diarrhea for a few weeks. The mentioned symptoms occurred following the injection of the Sinopharm/BBIBP COVID-19 vaccine. Due to the presence of pneumoperitoneum on chest radiography, the patient was transferred to the operating room with a diagnosis of generalized peritonitis and underwent midline laparotomy. On exploration of the abdominal cavity, the colon was perforated at two points: the sigmoid colon and the transverse colon. Signs of inflammation were observed around the perforated edges, but not elsewhere. The patient underwent an extended left hemicolectomy with end colostomy. The postoperative pathology report was consistent with CD, showing transmural chronic inflammation, deep fissuring ulcers, and cryptitis in the surgical specimen. Additionally, the immunohistochemical study for CMV was positive.

Discussion: Inflammatory bowel disease (IBD) is a chronic gastrointestinal inflammatory disease with a wide spectrum of extraintestinal manifestations. Due to the incidence of IBD and Guillain-Barré syndrome in the mentioned patient following vaccination, there is a possibility of the same pathogenesis for both diseases. The incidence of Guillain-Barré syndrome as one of the extraintestinal complications of IBD has been reported in numerous studies as a result of the coexistence of both diseases. Also, according to the recent history of vaccination in a previously healthy individual, it is possible to justify the association of Guillain-Barré syndrome and IBD with the vaccine. So far, many studies have reported the development of Guillain-Barré syndrome following vaccination, but to the best of our knowledge, no studies have reported IBD following Covid-19 vaccination yet. Another issue in this patient was the complication of Crohn's colitis with CMV. Despite the 7-8-fold higher incidence of CMV infection in patients with IBD, the role of CMV infection in Crohn's colitis has not been determined.

Keywords: Covid-19 Vaccination- Guillain-Barré Syndrome-Inflammatory Bowel Disease-Cytomegalovirus-Adverse Effects

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Introduction

Since the beginning of the Covid-19 pandemic in 2019, several vaccines have been manufactured around the globe. There have been concerns about the safety of these vaccines due to the production of new mRNA-based vaccines and the lack of time to complete the clinical trials. Injection site pain, headache, fatigue, fever, and malaise are the most frequent local and systemic complications in numerous studies, respectively [1]. The pooled rate of systemic complications in different studies has varied between 30-80% [1,2]. Overall, complications are less reported in inactivated and DNA vaccines compared to RNA vaccines [1,2]. Common gastrointestinal and neurological complications of Covid-19 vaccination have been reported in various studies, including diarrhea, abdominal pain, nausea, vomiting, dizziness, headache, myalgia, peripheral neuropathy, and demyelinating diseases [3-7]. In this article, the complications include Guillain-Barré syndrome and Crohn's disease that occurred following the injection of the Sinopharm/BBIBP COVID-19 vaccine.

Furthermore, in this patient, the course of Crohn's disease appeared to be exacerbated by Cytomegalovirus (CMV). CMV is a member of the Betaherpesvirinae subfamily of the Herpesviridae family; a well-known pathogen that often occurs in immunocompromised patients. The association between CMV infection and inflammatory bowel disease (IBD) has been reported in numerous studies. Whether the presence of CMV could lead to IBD or act as an exacerbating factor is not yet fully discovered. CMV presence in involved tissues of IBD patients was described by Dimitroulia et al [8]. Out of 85 patients diagnosed with IBD (58 ulcerative colitis patients and 27 Crohn's disease patients), 31% of ulcerative colitis patients and 18.5% of Crohn's disease patients were positive for CMV by polymerase chain reaction (PCR) test [8]. CMV is often considered a factor of steroid resistance in IBD patients [9]. However, as discussed below, CMV does not play a significant role in exacerbating or complicating Crohn's disease, unlike UC.

Case Presentation

The patient was a 36-year-old Caucasian male who presented with severe generalized abdominal pain, nausea, vomiting, fever, dyspnea, and fatigue 4 days prior to admission. The patient was complaining of watery diarrhea for a month. There was no history of similar symptoms in the past. He had been hospitalized due to bilateral ascending paraparesis and weakness, which was diagnosed as Guillain-Barré syndrome 2 weeks after receiving the Sinopharm/BBIBP COVID-19 vaccine. Other than his recent hospitalization, his past medical and surgical history was unremarkable. There was no recent history of any relevant medical procedures such as enema or colonoscopy. Considering his diagnosis of Guillain-Barré syndrome, he was admitted to the intensive care unit and administered intravenous immunoglobulin (IVIg). After a week, he was discharged, having achieved full recovery. He did not mention using any medications or illicit drugs. In physical exams, he was lethargic, vital signs were stable, and his temperature was detected at 38.2°C orally. The abdominal exam was consistent with peritonitis, presenting with generalized tenderness, rebound tenderness, and involuntary guarding.

Chest X-ray revealed pneumoperitoneum. Therefore, the patient was transferred to the operating room and a midline laparotomy was performed. After the initial exploration of the peritoneal cavity, two circumferential perforated lesions were detected: one in the mid part of the sigmoid colon and another in the mid part of the transverse colon. Both lesions had macerated edges (Figure 5).

There were no signs of ischemia or tumoral lesions. There was no discoloration, peristalsis and mesenteric pulses were present, and marginal bleeding was present as expected. Signs of inflammation such as tissue erythema and edema were present in the affected parts of the colon but not elsewhere. Fat creeping was not present. The patient underwent an extended left hemicolectomy with end colostomy. Postoperative histopathology examination revealed an increasing number of plasma cells and

Table 1. Patient`s lab data

Time of admission				
White cell count	**13.6 (×10³/µl)**	**C reactive protein (quantitative)**	**136 (mg/l)**
hemoglobin	8.8 (gr/dl)	Erythrocyte sedimentation rate-1hr	113 (mm/h)
Platelet count	219 (×10³/µl)	Blood culture	Negative for a week
neutrophils	92 (%)	lymphocytes	6.3 (%)

lymphocytes in the lamina propria with neutrophilic inflammation, cryptitis, and crypt abscesses (Figure 2). Architectural distortion, fissure formation, and inflammatory extensions to the muscular layer were also present (Figures 2, 3). Granuloma was not detected. The mentioned features were suggestive of inflammatory bowel disease, particularly Crohn's disease. To investigate cytomegalovirus infection, we used immunohistochemistry techniques such as clone CCH2, DDG9, and 1/50 dilution (DAKO). Immunohistochemical examination revealed the presence of enlarged endothelial cell nuclei, which contained inclusions of cytomegalovirus (Figure 4). The distribution of the cells positive for CMV was heterogeneous.

Discussion

Inflammatory bowel disease (IBD) is a chronic inflammatory disease that mainly involves the gastrointestinal tract. It also presents with a wide spectrum of extraintestinal manifestations involving the skin, eyes, joints, hepatobiliary system, etc. Whenever extraintestinal manifestations of IBD are discussed, the relationship between these manifestations and the disease activity is noted,

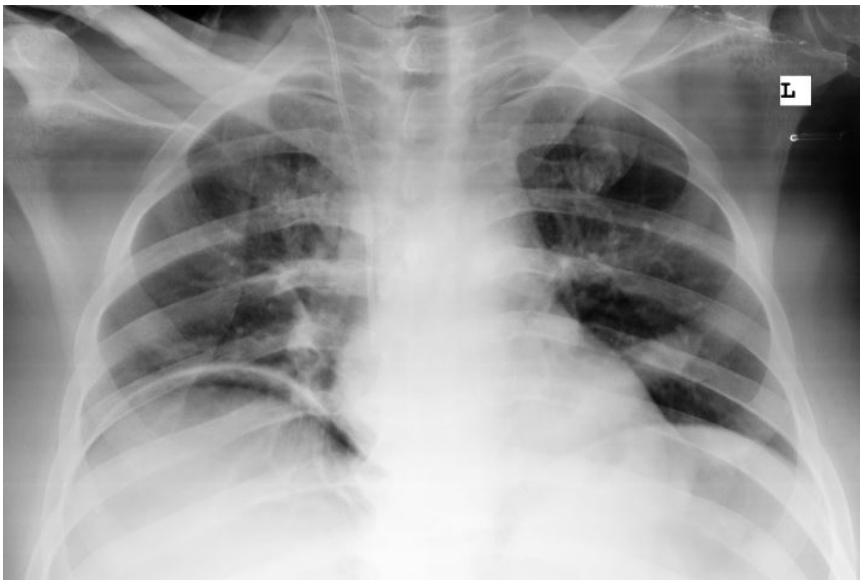

Fig. 1. Plain radiography of the chest

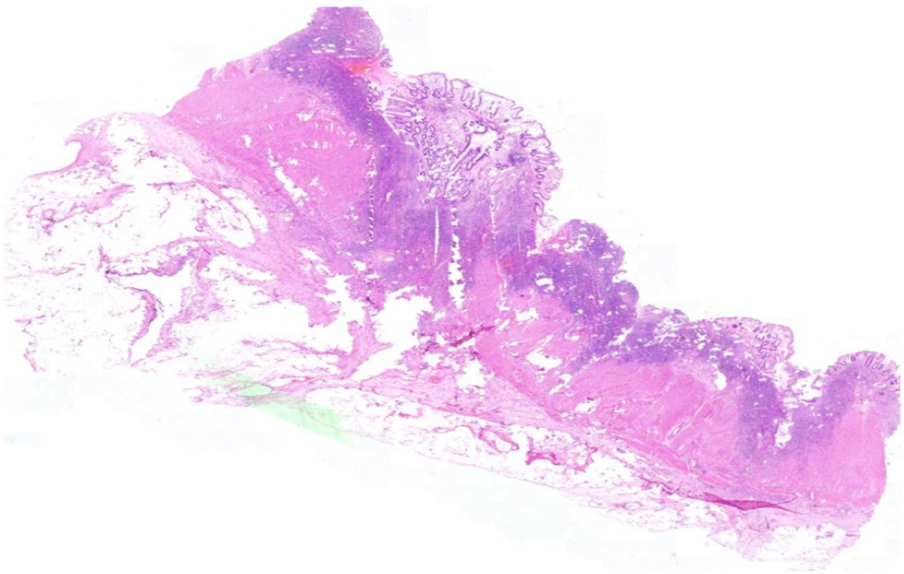

Fig. 2. Abundant inflammatory infiltration presents at the basis of glands and also in the lamina propria, composed predominantly of lymphocytes and plasmocytes (HE staining)

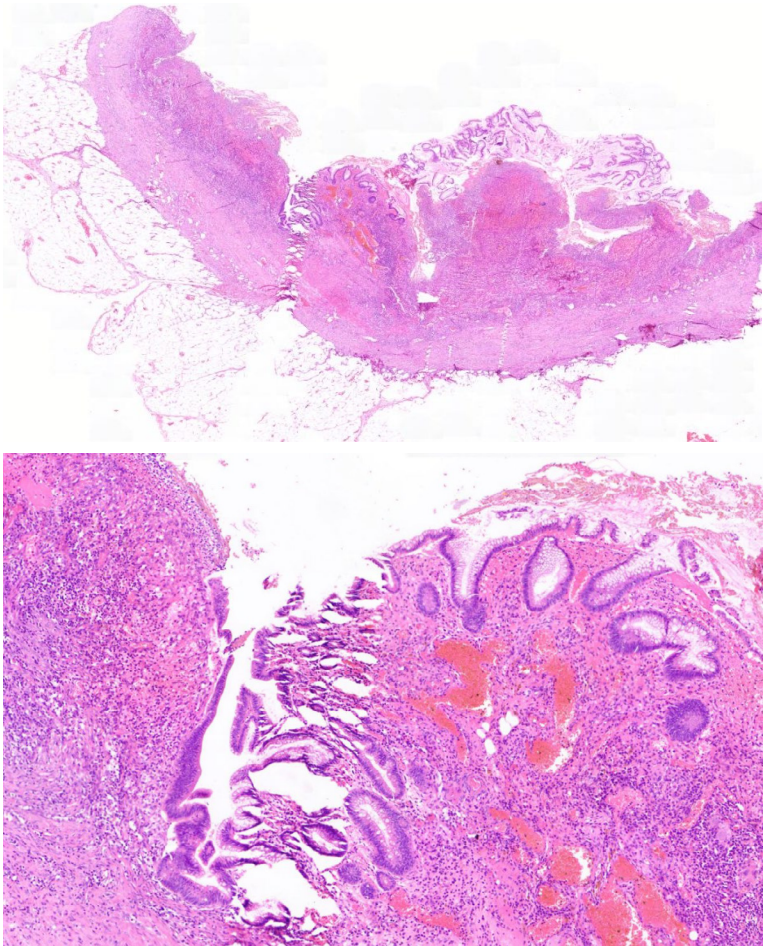

Fig. 3. ***

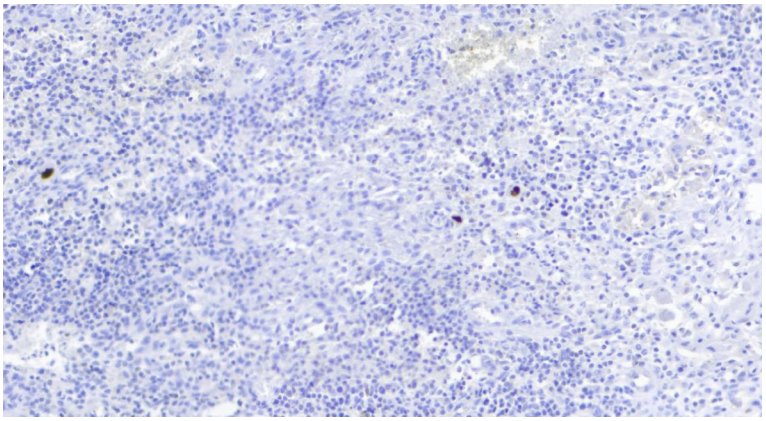

Fig. 4. Endothelial cells with positive inclusions of CMV and Anti-CMV antibodies

which divides them into two categories: those associated with disease activity and those which are not [10]. Out of the usual extraintestinal manifestations of IBD, neurologic complications are rather rare. The cause-and-effect relationship between neurologic signs and symptoms and IBD is not fully discovered yet. Malnutrition, immune-based reactions, drug-induced adverse effects, and thromboembolism have been mentioned to justify the association [3]. Also, recent use of biological drugs such as anti-tumor necrosis factor-alpha (TNF-α) has been recognized as effective, causing some of the mentioned side effects such as peripheral neuropathy, demyelinating diseases, or progressive multifocal

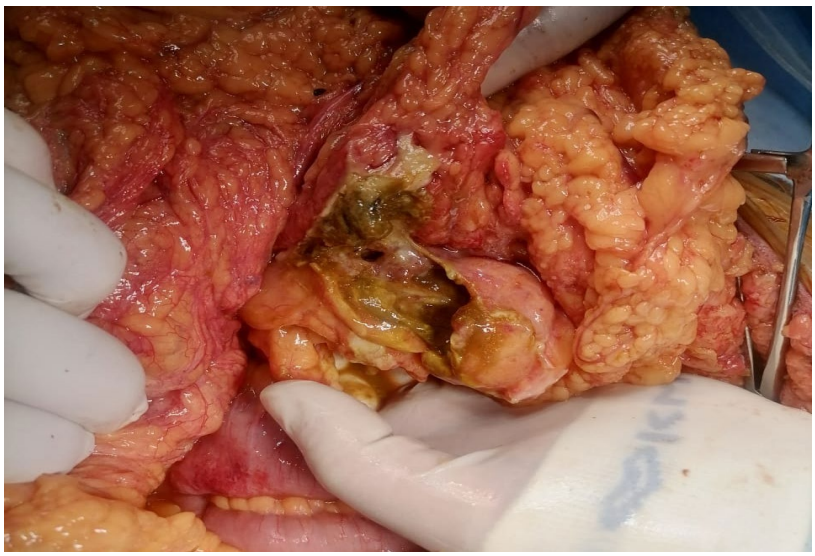

Fig. 5. Sigmoid colon lesion

leukoencephalopathy [3]. An MRI-based study reported hyperintense focal white-matter lesions in 42% of patients with Crohn's disease and 46% of patients with ulcerative colitis [11]. Some studies consider peripheral neuropathy as the most common neurologic complication among IBD patients. In contrast, other studies have identified demyelinating diseases to be more frequent [3,4]. The most frequent neurological complications are reported based on the Vaccine Adverse Event Reporting System (VAERS) as dizziness, headache, pain, muscle spasms, myalgia, and paresthesia [7]. In addition, findings from VAERS indicate rarer neurological complications, including stroke, facial palsy, transverse myelitis, GBS, and acute disseminated encephalomyelitis [7].

Treatment with biological agents could be considered as a precursor to demyelinating diseases such as GBS in patients with IBD [12] [13].

Due to the SARS-CoV-2 pandemic status and the necessity of mass vaccination for disease control, various types of vaccines have been manufactured. In this case report, our patient's symptoms started after receiving the first dose of the Sinopharm/BBIBP COVID-19 vaccine. Inactivated vaccines have traditionally been used to provide immunity by producing antibodies. Since 2019, numerous studies have been conducted to investigate the association between Covid-19 vaccination and possible adverse effects. Neurologic adverse effects such as Guillain-Barré syndrome, venous sinus thrombosis, headache, transverse myelitis, and multiple sclerosis have been reported in numerous studies following Covid-19 vaccination [14]. The association between SARS-CoV-2 infection and Guillain-Barré syndrome (GBS) has been reported in several case reports [15]. It is believed that GBS occurs due to a cross-immunity reaction to a foreign antigen followed by an infection or vaccination. Previous studies have demonstrated an association between GBS and severe acute respiratory syndrome (SARS). Due to the common origin of SARS and SARS-CoV-2 in the Coronaviridae family, SARS-CoV-2 may also be associated with GBS. Post-vaccination GBS has been reported in case-based studies repeatedly. It can also manifest after receiving mRNA vaccines, vector-based vaccines, or inactivated vaccines [16].

A large-scale study reported 11 cases diagnosed with GBS after receiving ChAdOx1 nCoV-19 and 5 or fewer cases after receiving BNT162b2 and mRNA-1723 vaccines [16]. Another study on 721,588 Hong Kong residents receiving BNT162b2 or CoronaVac vaccines reported post-vaccination GBS in 5 or fewer cases receiving BNT162b2 and none of the cases receiving the CoronaVac vaccine, which was statistically insignificant compared to non-vaccinated individuals [17]. In contrast, gastrointestinal adverse effects after vaccination have been reported more commonly. Diarrhea, abdominal pain, nausea, and vomiting are the most prevalent GI adverse effects [5,6].

Theoretically, preexisting conditions such as IBD could be affected by vaccination. In a study, 3272 patients with IBD who underwent Covid-19 vaccination (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2-S) were analyzed retrospectively. IBD-related adverse reactions in these patients were insignificant [18]. Botwin et al. studied 246 IBD patients (67% with CD, 33% with ulcerative or indeterminate colitis) who had received BNT162b2 (57%) or mRNA-1273 (42.7%) vaccines [19]. The most prevalent systemic adverse effect was fatigue and malaise (23% after the first dose and 45%

after the second dose). Vaccine-related adverse effects were less common in patients over 50 years of age and those who were treated with immunomodulating agents. Only one patient was hospitalized due to severe gastroenterological symptoms after receiving the second dose of the vaccine [19]. Considering the immunological pathogenesis of Guillain-Barré syndrome and IBD, active immunization could eventually lead to both diseases by starting a chain of immunological events.

Another issue reported in the presented patient was the complication of the disease course with CMV. CMV is a ubiquitous DNA virus of the Herpesviridae family. CMV seroprevalence was reported between 60-90% in the general population depending on age and ethnicity [20]. A systematic review analyzed 290 non-immunocompromised patients who presented with severe CMV infection. The gastrointestinal tract was the most common site of involvement by CMV, causing gastroenteritis, duodenitis, ileitis, colitis, etc. [21].

In the case of CMV colitis, the relationship between CMV infection and other etiological factors of colitis such as inflammatory bowel disease (IBD) should be considered. Due to the administration of anti-inflammatory agents such as corticosteroids, IBD patients are often considered immunocompromised individuals and susceptible to CMV infection. CMV infection incidence has been reported to be 7-8 times higher in IBD patients [8]. Some studies have described the association between CMV and severe ulcerative colitis (UC). A study conducted on 120 patients demonstrated a prevalence of 25% for CMV infection in refractory UC compared to 2.5% in non-refractory UC [22]. Another study conducted on 95 IBD patients and 50 healthy control subjects reported a higher prevalence of mucosal CMV DNA in the IBD group [23]. Also, the role of CMV infection in acute severe ulcerative colitis was investigated in another study. Out of 149 patients with acute severe ulcerative colitis, 50 (33.6%) were diagnosed with CMV colitis [24]. In a meta-analysis with a higher sample size, the rate of resistance to corticosteroids in the IBD-CMV positive group compared to the IBD-CMV negative group was 52.9% versus 30.2% [25]. Therefore, CMV can be mentioned as one of the factors of resistance to treatment with corticosteroids in patients with IBD.

Contrary to UC, the relationship between Crohn's disease (CD) and CMV infection has remained indeterminate. A retrospective study by Kim et al. was done on 122 UC patients and 20 CD patients who presented with acute exacerbation of IBD. CMV infection was detected in 10% of UC patients and none of the CD patients by immunohistochemical staining [26]. In a study, 16 patients diagnosed with Crohn's disease who underwent elective or emergent surgical intervention were investigated for CMV infection by immunohistochemical staining on surgical specimens, which was negative in all cases [27]. In another study among 10 patients diagnosed with resistant CD, none were involved by CMV infection [28]. Therefore, it could be concluded that CMV infection is hardly considered a factor for exacerbation of CD.

Conclusion

As we observed in this case, the patient presented with a clinical manifestation of peritonitis and was diagnosed with fulminant Crohn's colitis retrospectively, based on a postoperative pathology report. During the surgery, two large circumferential perforated lesions were found in the sigmoid and transverse colon with no signs of obvious inflammation. Due to the proper appearance of the proximal parts of the colon, without comprehending the diagnosis of CD, the patient underwent an extended left hemicolectomy and end colostomy. The postoperative pathology report was consistent with the diagnosis of Crohn's colitis associated with CMV infection.

Given that all of the patient's symptoms developed shortly after the Sinopharm/BBIBP COVID-19 vaccination in a previously healthy young individual, it is not unreasonable to consider vaccination as a triggering event. GBS occurred about 2 weeks and acute watery diarrhea 3 weeks after vaccination, respectively. As we discussed earlier, GBS is considered both one of the extraintestinal manifestations of IBD and one of the most frequent neurologic adverse effects following COVID-19 vaccination. In the case of CD, it is not possible to conclude with certainty whether the COVID-19 vaccination caused the disease or whether it occurred accidentally.

Another issue is the association of CMV infection with Crohn's colitis, which, as previously described, is almost non-existent. Due to the association of various factors in this patient, any conclusion regarding the association should be carefully studied.

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