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Correspondence

SARS-CoV-2 infection in severe pediatric Crohn's disease. What about anti-tumor necrosis factor α therapy?


Dear Editor,

We report the case of a 17 years-old female patient, affected by COVID-19 and under anti-TNF α treatment with adalimumab for severe Crohn's disease. She was diagnosed 10 years ago with a severe ileal and perianal complex Crohn's disease (Paris classification A1a L1 B1 P G0).

She then underwent multiple perianal surgeries, and, over the years, was treated with exclusive enteral nutrition and thiopurines, then with infliximab, which was suspended for adverse reaction, and lastly with adalimumab. She had good clinical response to anti-tumor necrosis factor (TNF) α therapy, despite the development of vulvar metastatic Crohn's disease, treated with local clobetasol. Adalimumab was suspended after 2 years due to sustained clinical remission associated with anal stenosis.

In February 2020, 6 months after stopping adalimumab, the patient experienced a severe recurrence of symptoms with endoscopic evidence of severe rectal disease activity. Therefore, on February 21st, just before the announcement of the first case of SARS-CoV-2 infection in Italy, adalimumab was resumed, with standard induction doses, followed by maintenance subcutaneous administration of 40 mg e. o. w. She had a good disease control, except for the persistence of anal irritation dermatitis and metastatic vulvar Crohn's disease treated and topical clobetasol, respectively. The patient was waiting for elective surgical correction of residual anal stenosis. The last dose of adalimumab was administered on April 18th. On April 21st, the patient developed low-grade fever (less than 37,5°C) and fatigue, which were initially misinterpreted as Crohn's disease manifestations. On April 27th, before being admitted to the hospital for surgery, a naso-pharyngeal swab for SARS-CoV2 was made which turned out to be positive. The COVID-19 course was then characterized by a single episode of fever (TC 38,5°C), which resolved on April 30th. Mild exertional dyspnea lasted for three days, but she always had normal thoracic examination and oxygen saturation at rest and during the 6 min walking test. As Crohn's disease was in clinical remission, we decided to suspend the adalimumab administration of May 1st, waiting for the COVID-19 course. On May 6th the patient experienced a relapse of fatigue and metastatic vulvar disease despite topical treatment. On May 11th, she performed a second naso-pharyngeal swab, which turned out to be negative. After receiving the result, on May 15th, adalimumab was resumed with rapid improvement of both fatigue and metastatic Crohn's disease. Another naso-pharyngeal swab was performed one week later, again with a negative result. Of note, our patient's parents were asymptomatic and tested negative for SARS-CoV-2.

During the SARS-CoV-2 pandemic, conflicting opinions have been expressed on the use of immunomodulatory therapy in patients with inflammatory bowel diseases (IBD). The recent guidelines of the Pediatric IBD Porto Group [1] recommend not to interrupt anti-TNF α therapy except in case of acute febrile illness, irrespective of SARS-CoV-2 testing status, until the child returns to normal health. Recent evidence from the SECURE-IBD international database [2] suggests that the use of anti-TNF α monotherapy does not increase the risk of severe SARS-Cov-2 infection (aOR 0.9, 95% CI 0.4–2.2), as steroids (aOR 6.9, 95% CI 2.3–20.5), mesalamine/sulfasalazine (aOR 3.1, 95% CI 1.3–7.7) and combination therapy with thiopurines (aOR 5.0, 95% CI 2.0–12.3) seem to do. Indeed, anti-TNF α therapy could play an important role in the treatment of severe forms of COVID-19 [3]. To date the SECURE-IBD database consists of 1302 patients of which 61 (4,7%) are younger than 20 years, and only 4 (0,3%) belong to the 0–9 age range [4]. These data support the protective role of young age against severe forms of COVID-19 even in patients with IBD [2]. Moreover, patients with IBD do not seem to have an overall greater risk of SARS-COV-2 infection nor of an unfavorable course of COVID-19 [5]. To date, in our third level Pediatric Gastroenterology Unit we follow 116 patients, of which 30,2% are treated with an immunosuppressive drug and 34,5% are on a biologic monotherapy. Up to June 1st there were no cases of suspected COVID-19, even among 2 patients with ascertained close contact with an infected person, except for the one described above. She had a mild form of COVID-19 with a favorable outcome, although the onset of symptoms occurred shortly after the administration of adalimumab. The suspension of this therapy close to the febrile rise, as indicated in the pediatric guidelines [1] not only did not accelerate the healing, which was evidently already underway, but could also have led to a flare of Crohn's disease. Another challenge was to suspect that the non-specific initial symptoms were not related to Crohn's disease but rather to the COVID-19. In fact, COVID-19 can occur in a non-classical form with gastrointestinal manifestations such as diarrhea, vomiting, and abdominal pain, not always in association with classic respiratory symptoms. Garazzino et al. described diarrhea in 22 (13,1%) and vomiting in 9 (5,4%) of 168 SARS-CoV-2 infected Italian children [6]. It appears thus appropriate, in this historical period, to include in the differential diagnosis of a suspected IBD recurrence, not only "typical" infectious agents (i.e. Cytomegalovirus, Clostridium Difficile, and so on), but also SARS-CoV2 infection with a gastrointestinal expression [7]. And what about a mass screening for SARS-CoV-2 infection before starting biological therapy in patients with IBDs, as suggested by Zingone et al. [8]? Even if the strict social distancing certainly played an important role in the low incidence of COVID-19 and in the absence of severe COVID-19 among our patients, our little monocentric experience is part of a growing amount of data in the

literature which does not show a higher incidence, compared to the general population, of COVID-19 in patients with IBD even on immunomodulatory therapy. Furthermore, the data of a favorable disease course in young subjects, particularly in children, is being confirmed worldwide. Since the identification of the first COVID-19 case, on February 21st, 2020, the burden of SARS-CoV-2 infection has spread in Italy. Up to June 1st there have been 232,997 ascertained cases with 33,415 deaths [9]. Up to May 22nd, there were 4,922 SARS-CoV-2 infections in patients under 20 years of age, with 3 deaths and no ICU admissions.

It would therefore seem that, in pediatric and young patients, anti-TNF α therapy can be performed safely even during mild COVID-19. The immunosuppressive effects of anti-TNF α medications may persist for many weeks after treatment cessation. This, together with the low sensitivity of the naso-pharyngeal swab [10], indicates that there is currently no greater need to screen for SARS-CoV-2 asymptomatic pediatric patients about to start such therapy unless they had either contact with an infected person or suspected symptoms for COVID-19 in the previous period. Of course, all these statements need confirmation in large cohort studies.

Declaration of Competing Interest

There are no conflicts of interest to disclose

Financial Disclosure

There are no financial conflicts of interest to disclose

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