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RESEARCH LETTER

Refractory celiac disease and COVID-19 outbreak: Findings from a high incidence scenario in Northern Italy



Introduction

During the last months, the world assisted to the dramatic SARS-CoV-2 (severe acute respiratory syndrome-coronavirus 2) pandemic and, unfortunately, Northern Italy and the Milano urban area resulted one of the most infected zones. SARS-CoV-2 infection is frequently asymptomatic, but in a certain percentage of cases (roughly 30–50%) it causes Covid-19 (Coronavirus disease 2019) which is characterized in the worst cases by pulmonary distress syndrome with high mortality rates [1]. Beyond lungs, the clinical picture of Covid-19 can present gastrointestinal symptoms such as nausea, vomiting and diarrhea. Although the origin of these symptoms is not clear, it is well known that angiotensin converting enzyme 2 (ACE2) receptor (the protein that the virus uses to get into the cell) is present also on luminal surface of the enterocytes: therefore, it seems plausible that SARS-CoV-2 might also infect the gastrointestinal tract and, in particular, the small bowel (SB) [2]. Furthermore, SARS-CoV-2 RNA has been found also in the stool of Covid-19 patients [3]. According to the WHO guidelines, diagnosis of Covid-19 is confirmed by the reverse transcription polymerase chain reaction (RT-PCR), performed on samples from the respiratory tract, e.g., nasopharyngeal swabs. Different factors, including hypertension, cardiologic disorders, overweight, smoking habits, male sex and diabetes mellitus increase the hospitalization risk and worsen the prognosis of Covid-19 patients; there is still doubt whether the presence of any immunological disorder is a risk factor for Covid-19 [4,5].

Among immunological disorders, celiac disease (CD) is one of the most common, usually efficiently treated with a gluten free diet (GFD) and with an optimal prognosis. From the other hand, Refractory Celiac Disease (RCD) is a rare complication of CD characterized by persistent or recurrent malabsorptive symptoms and/or signs with villous atrophy despite a strict GFD for more than 12 months in the absence of other causes of villous atrophy or malignant complications [6,7]. It can be subdivided into two forms

(RCD-I and RCD-II) on the basis of the immunophenotype of intraepithelial lymphocytes (IELs), but this classification is not always straightforward [8,9].

With the present study, we aimed to verify the presence of Covid-19 and/or SARS-CoV-2 infection in an Italian cohort of patients with RCD.

Methods

We enrolled patients with RCD followed in our third level Celiac Disease Center, located in Milano (Centro per la Prevenzione e Diagnosi della Malattia Celiaca, Fondazione IRCCS Ca' Granda). Diagnosis of RCD, type I or II, has been based upon the international guidelines [10]. In particular, cytofluorimetry of duodenal biopsies has been performed to define the percentage of aberrant IELs presenting the intracytoplasmic form of CD3 and, together with the T-cell receptor γ (TCR γ) rearrangement; these two biomarkers have been adopted to discriminate between RCD-I and II.

For each patient we recorded the following clinical and demographic data: age, age at the diagnosis of CD and RCD, sex, type of RCD, last duodenal histology (Marsh-Oberhuber classification), presence of aberrant IELs, TCR γ rearrangement, compliance to GFD (nutritionist and urine gluten peptide detection) and ongoing treatment.

From 20th to 24th April 2020, RCD patients were called. The following items (referred to the previous two months of lockdown) have been recorded: presence of Covid-19 symptoms (such as fever, cough, dyspnea, nausea, vomiting, diarrhea and neurological symptoms) [11] or a Covid-19 cohabitant, hospitalization, SARS-CoV-2 PCR test results if available, compliance with social distancing and shielding recommendations.

Results

Twenty-one patients living in the Milano area were contacted, 16 females, age 53.2 ± 15.3 years, age at diagnosis of CD 50.0 ± 13.5 years, age at RCD diagnosis 54.5 ± 15.5 years. Nine were classified as RCD-I and twelve as RCD-II. No differences about sex distribution and age, age at CD and RCD diagnosis have been evidenced between the two

Table 1 Characteristics of patients with refractory celiac disease.

Sex	Age (Y)	Age at CD diagnosis (Y)	Age at RCD diagnosis (Y)	RCD type	Duodenal histology	Aberrant IEL (%)	Immunological comorbidities	Other comorbidities	TCR γ	Compliance to GFD	Therapy	Covid-19 symptoms	Antiviral lifestyle
F	63	49	50	2	3c	Unknown	SLE, autoimmune hepatitis, mycosis fungoides	Osteoporosis	Monoclonal	Optimal	Azathioprine Corticosteroids	No	Yes
F	46	39	40	2	3b	82	Erythema nodosum	—	Monoclonal	Optimal	Budesonide	No	Yes
M	56	44	48	1	3c	10	—	Arterial hypertension	Policlonal	Optimal	—	No	Yes
F	63	61	64	1	3c	0	—	Osteoporosis	Policlonal	Optimal	—	No	Yes
F	45	39	40	1	3b	0	Autoimmune thyroiditis, collagenosis colitic	—	Policlonal	Optimal	Budesonide	No	Yes
F	77	70	73	1	3a	0	—	Osteoporosis	Policlonal	Optimal	Budesonide	No	Yes
F	62	53	58	2	3b	0	—	HBV hepatitis, osteoporosis	Monoclonal	Optimal	Budesonide	No	Yes
M	63	62	63	2	3c	33	Lymphocytic colitis	Thalassemic trait	Policlonal	Optimal	Budesonide	No	Yes
F	30	26	28	1	3a	0	—	—	Policlonal	Optimal	—	No	Yes
F	75	68	70	1	3a	0	Autoimmune hyperparathyroidism	Osteoporosis, rectal carcinoma	Policlonal	Optimal	—	No	Yes
F	42	32	39	2	3c	0	—	—	Monoclonal	Optimal	Budesonide	No	Yes
M	62	61	62	2	3c, UJ	25	Autoimmune thyroiditis	—	Policlonal	Optimal	Azathioprine	No	Yes

Table 1 (Continued)

Sex	Age (Y)	Age at CD diagnosis (Y)	Age at RCD diagnosis (Y)	RCD type	Duodenal histology	Aberrant IEL (%)	Immunological comorbidities	Other comorbidities	TCR γ	Compliance to GFD	Therapy	Covid-19 symptoms	Antiviral lifestyle
F	66	62	63	2	3c, UJ	60	—	—	Monoclonal	Optimal	Budesonide cladribine	No	Yes
M	77	64	69	2	3c	85	Purpura	Osteoporosis, HBV hepatitis	Monoclonal	Optimal	Budesonide cladribine	No	Yes
F	53	46	48	1	3a	0	—	Asthma	Policlonal	Optimal	—	No	Yes
F	69	50	68	2	3a	44	Collagenosic colitis	Osteoporosis	Monoclonal	Optimal	Budesonide	No	Yes
F	51	51	53	2	3a	0	—	Osteoporosis	Policlonal	Optimal	—	No	Yes
F	76	76	80	2	3b	81	Autoimmune hepatitis	Osteoporosis, secondary hyperparathyroidism	Monoclonal	Optimal	Budesonide	No	Yes
M	52	52	52	2	3c	40	—	—	Monoclonal	Optimal	Budesonide	No	Yes
F	35	35	36	1	3c	0	—	Osteoporosis	Policlonal	Optimal	—	No	Yes
F	36	36	38	1	3a	40	—	Osteoporosis	Monoclonal	Optimal	Budesonide	No	Yes

UJ: ulcerative jejunoileitis. SLE: systemic lupus erythematosus. HBV: hepatitis B virus.

groups. All duodenal histologies presented atrophy without differences at Marsh-Oberhuber classification between RCD-I and II; however, 2 RCD-II patients presented ulcerative jejunoileitis. Compared to RCD-I, RCD-II patients more frequently took drugs ($p=0.01$) included cladribine. At least one immunological comorbidity was present in 22% (2/9) of RCD-I patients and 58% (7/12) of RCD-II; globally 3 immunological disorders were present in RCD-I and 12 in RCD-II.

None of the 21 RCD patients reported symptoms suggestive of Covid-19 or change of their symptoms in the analysed period, no cohabitants developed Covid-19; consequently, none was hospitalized or underwent PCR testing.

Table 1 shows the characteristic of the RCD patients.

Discussion

Despite of the severe clinical picture and fragility of patients with RCD type I and II, none of them developed Covid-19 in spite the high incidence of SARS-CoV-2 infection in the Milano area. Although with several limitations, these findings give hope for those patients affected by a severe form of CD and clinicians who are responsible of the RCD patients.

Numerous studies have investigated the theoretical increased risk of infections, both viral and bacterial, in celiac patients.

Regarding viral infections, the presence of the HLA-DQ2.5 heterodimer (from now on indicated as DQ2), which is an HLA class II molecule essential for antigen presentation to CD4+ T helper lymphocytes, seems to play a key role. This particular HLA molecule characterises about 90% of celiac patients and 25–30% of the Caucasian population. It has been shown that DQ2 has a reduced ability to interact with T helper cells and this could influence the antiviral response of DQ2 positive individuals. Furthermore, it has been noted that the presence of DQ2 is associated to a lower response to vaccination, in particular that against Hepatitis B virus. Notably, peripheral blood mononuclear cells isolated from DQ2 positive vaccinated children exposed to HBV, show a lower cytokine production with reduced expression of IL4 and IFN γ [12,13].

It is not clear if this could increase the susceptibility to SARS-CoV-2 infection, also in the light of recent studies indicating the absence of risk to develop influenza or herpes zoster independently of the presence of an active celiac disease (*i.e.* villous atrophy at duodenal histology).

In respect of susceptibility to bacterial infections, a general increased risk of sepsis, mostly pneumococcal, has been found in CD patients and seems connected to hyposplenism. The spleen has an extremely important immune role, maintaining the pool of IgM memory B-cells (CD27+) which are developed in the marginal zone; those memory B-cells warrant a T-independent response against encapsulated bacteria. Hyposplenism is a condition with an estimated prevalence in celiac patients of 19–80% and leads to a deficient immune response against encapsulated bacteria (mainly *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Hemophilus influenza*). It affects only adult celiac patients and it seems to correlate with the exposition to gluten: the longer the patient has been exposed to diets containing gluten, the higher is the probability of develop it [14].

Focusing on Covid-19, the susceptibility to bacterial infections could play a role; in fact, it has been recently reported that the prevalence of co-infections in Covid-19 patients could be up to 50%, especially among non-survivors. Co-pathogens include fungi, viruses and bacteria such as *Streptococcus pneumonia* [15].

Starting from the point that CD patients may present a slightly increased risk of infections, when it comes to RCD, it is reasonable to consider it highly susceptible, being RCD, and especially type II, graced by a severe prognosis and a complicated clinical picture. The most common symptoms of RCD are diarrhea, abdominal pain, involuntary weight loss, general malaise, anemia, hypoalbuminemia, vitamin deficiencies and concomitant autoimmune disorders [16]. Malnutrition due to protein-losing enteropathy can be severe, compromising the patient's performance status. Furthermore, RCD can encounter complications such as ulcerative jejunoileitis and T-cell lymphoma, driving to a leaky gut condition promoting the passage of pathogens from the lumen to the bloodstream [6]. Again, as in our cohort, RCD patients frequently assume immunosuppressive (azathioprine) and/or chemotherapeutic agent (cladribine). All these aspects can lead to an impaired immune response and magnify a pre-existing susceptibility to infections.

The findings of the present study appear in line with those emerging from IBD cohorts [17,18]; in fact, IBD patients living in high incidence regions do not appear particularly involved by the SARS-CoV-2 infection, although some cases of death in IBD patients and Covid-19 have been reported and the issue remains unclear. Following the novel British Society of Gastroenterology (BSG) IBD guidelines for Covid-19, some of the RCD patients should be posed in a high level of risk in case of SARS-CoV-2 infection due to the administration of relevant immunosuppressive drug; other assuming topic corticosteroids could be considered in a lower class of risk [17].

Different reason could explain the apparent safe state of the patients affected by RCD beyond their immunologic state: RCD patients referred to strictly follow an "anti-virus" lifestyle, in other words, they applied the social distancing and the shielding rigorously; this is due to the consciousness to have a severe disease and the fear to develop a fatal form of Covid-19. This attitude could be present also in CD patients with comorbidities [19] or in patients with other chronic diseases as IBD.

Although conducted in a high incidence scenario, notably, our study involves only a few number of patients; however, it should be kept in mind that RCD is a rare disorder and thus the possibility to have high number of patients can be reached only in case of large multicenter studies involving different countries and actually not available.

In conclusion, being aware about the limit of the present study, we observed an uneventful course in patients affected by RCD, assuming relevant therapies, reducing anxiety towards these fragile patients [20].

Ethics approval and consent to participate

The local Ethics Committee for Human Research of the City of Milan approved the study protocol (ref. no. 349_2020).

Enrolled patients gave their written consent to participate to the study.

Consent for publication

Not applicable

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Authors' contributions

L.E. (guarantor): interpretation of data, drafting and critical revision of the manuscript; L.S.: data extraction, interpretation of data, drafting and critical revision of the manuscript; M.V., L.D.: critical revision of the manuscript; A.S., V.L.: Data extraction.

Competing interests

None

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