Case report

Atypical manifestations of COVID-19 in general practice: a case of gastrointestinal symptoms

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Accepted 13 August 2020

SUMMARY

During the previous months, we have seen the rapid pandemic spread of SARS-CoV-2. Despite being considered a respiratory virus, it has become clear that other clinical presentations are possible and some of these are quite frequent. In this paper, a case of a man in his late 70s showing atypical symptoms in general practice is presented. Apart from fever, the patient complained of diarrhoea, borborygmus, loss of appetite and nausea. He developed no respiratory symptoms during his disease. Due to his symptoms, malignant disease was suspected, and he was referred for further testing which revealed typical COVID-19 findings on a chest CT scan. The occurrence of atypical symptoms is discussed, including the importance of recognising these in an ongoing pandemic.

BACKGROUND

In December 2019, a cumulation of patients with pneumonia of unidentified cause was registered in Wuhan, Hubei Province, China. Prior to this, six strains of human pathogenic coronaviruses had been identified. In February 2020, the WHO and the International Committee on Taxonomy of Viruses established the classification of the seventh human pathogenic virus SARS-CoV-2 as the disease causative agent of COVID-19.[1 2] While the name of the virus indicates respiratory disease, the ongoing pandemic has shown that COVID-19 is capable of causing symptoms from several organ systems, either concomitant with respiratory illness or as the only manifestation. Recognising the clinical characteristics of COVID-19, typical as well as atypical, is of high importance in the prevention of further spread of the virus. In this report, an atypical case of COVID-19 in general practice is presented. Furthermore, the significance of alternative manifestations is discussed.

CASE PRESENTATION

The case of a man in his late 70s is presented. The patient had a medical history of herpes zoster and stroke without sequelae. He first contacted his general practitioner in mid-March 2020 due to 9 days of fever which was gradually decreasing. Rectal temperature was 38.5°C. The patient's complaints were musculoskeletal body aches, influenza-like symptoms and headache. These symptoms had subsided at the time of initial contact. He also experienced rumbling of the stomach, diarrhoea, a general feeling of malaise and unease, weight loss, and night sweats. He denied shortness of breath, cough or other airway-related symptoms.

At the objective examination, the patient appeared tired and exhausted, but with normal awareness, contact and cerebral condition. There were no signs of respiratory distress, and respiratory frequency was 18 per minute. Examination of the eyes and oral cavity as well as auscultation of the heart and lungs were normal. There was no palpable lymphadenopathy in the head, neck and periclavicular regions. Abdominal inspection, palpation, percussion and auscultation were with normal findings. Laboratory results are presented in table 1. Blood pressure was 135/90 mm Hg, and pulse was estimated to be approximately 80 beats per minute. Urine dipstick showed trace of protein. The condition was diagnosed as a viral infection, and blood samples were collected for further testing. He was given a control appointment 3 days later.

At his control appointment, the patient reported poor appetite and nausea, and food intake was sparse. Otherwise, symptoms had remained the same with a continuous feeling of malaise. There was no stomach pain, but he had abdominal discomfort. His headache had diminished.

The objective examination was with unchanged general condition. The patient still appeared exhausted, but otherwise his respiratory condition and appearance were natural. Digital rectal examination revealed an enlarged and hard prostate with normal lateral boundaries. No faeces or blood was seen on the examination glove, and there was no pain on examination. There was an increase in C reactive protein (CRP) to 60, with a normal white and red blood cell count. Due to continuous diffuse symptoms, primarily abdominal discomfort and weight loss, the patient was sent for further investigations. This included occult cancer screening with thorough blood work and a CT scan of the throat, chest, abdomen and pelvis.

Two weeks after the onset of symptoms, the CT scan showed bilateral ground glass opacities (GGO) in the lungs, raising the suspicion of infectious or postinfectious foci. As a result of these findings, combined with the short history, fever and an increase in CRP, COVID-19 was thought of as a possible diagnosis. The patient was tested for SARS-CoV-2 with materials obtained from tracheal suctioning. The test came out positive for SARS-CoV-2 and negative for influenza virus and respiratory syncytial virus. In the mean time, the patient's condition had deteriorated, and he

To cite: Wahab SF, Løgstrup BB. *BMJ Case Rep* 2020;**13**:e237520. doi:10.1136/bcr-2020-237520

Table 1 Biochemical profile

Test	Value	Reference range
CRP (mg/L)	42 (day 1) 79.9 (day 5) 11.5 (day 12)	<8
Alanine aminotransferase (U/L)	73	10–70
Monocytes (×10^9/L)	0.84	0.2–0.7
Leucocytes (×10^9/L)	7.05	3.5–10
Neutrophils (×10^9/L)	4.66	2–7
Eosinophils (×10^9/L)	<0.02	<0.5
Basophils (×10^9/L)	<0.02	<0.1
Lymphocytes (×10^9/L)	1.51	1.3–3.5
Thrombocytes (×10^9/L)	221	145–350
Haemoglobin (g/L)	145	134–169
Erythrocyte sedimentation rate (mm/hour)	57	<20
Reticulocytes (×10^{12}/L)	0.029	0.036–0.113
Haptoglobin (g/L)	>3.4	0.47–2.05
Ferritin (µg/L)	2641	22–355
Transferrin (µmol/L)	18	24–41
Plasma iron (µmol/L)	3	9–34
Blood glucose (mmol/L)	5.4	4.2–7.8
Plasma creatinine (µmol/L)	87	60–105
eGFR (mL/min)	73	>60
Plasma kappa chain (Ig) (free) (mg/L)	36.4	3.3–19.4
Plasma lambda chain (Ig) (free) (mg/L)	23.1	5.7–26.3
Plasma kappa chain to lambda chain ratio (Ig) (free)	1.58	0.26–1.65
IgM (g/L)	0.15	0.39–2.08
High-density lipoprotein (mmol/L)	0.87	>1

Day 1 indicates first contact to general practice. CRP development is denoted, and the rest are results from day 5.
The following tests were normal: HbA1c, INR, potassium, sodium, alkaline phosphatase, total bilirubin, TSH, antinuclear antibodies, IgA, urate, alpha-fetoprotein, HBsAg, anti-HCV, HAV-IgM, folate, amylase, M component, IgG, cobalamin (B_{12}), PSA, albumin and human choriogonadotropin.
CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HAV, hepatitis A virus; HbA1c, Haemoglobin A1c; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio; PSA, prostate specific antigen; TSH, thyroid stimulating hormone.

felt unwell. Therefore, the doctor admitted the patient to the hospital at the COVID-19 isolation floor.

At admission, oxygen saturation was 93% without oxygen therapy. Furthermore, he had a respiratory frequency of 18 per minute, temperature of 37.8°C, blood pressure of 148/95 mm Hg and otherwise stable vital parameters. During the first 5 days of admission, he developed an oxygen demand of up to 3 L/min to uphold an oxygen saturation of 91%–95%. The patient was hospitalised for a total of 8 days. Throughout the course of the disease, he did not complain of regular sore throat, stuffy nose, sneezing, cough, dyspnoea or other airway-related symptoms.

INVESTIGATIONS

The suspicion of COVID-19 in our patient was raised by the radiology department. The chest CT scan was performed with arterial phase contrast. It mainly showed peripheral but also central peribronchovascular GGO. Streaky consolidations were seen in the right upper lobe. Multiple swollen lymph nodes were detected in the mediastinum and both lung hila. The key findings are presented in figures 1–4. There were insignificant laminar subsegmental atelectasis in the posterobasal areas of both lower

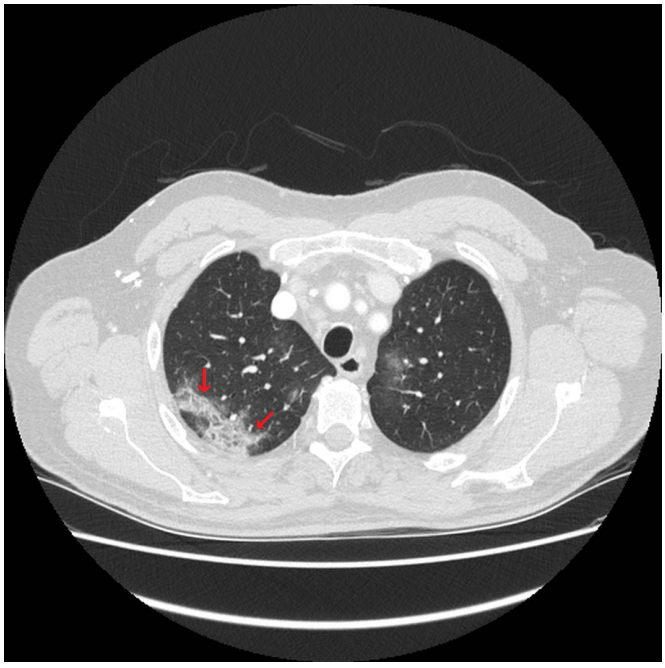

Figure 1 CT scan in axial plane showing streaky consolidations in the right upper lobe (arrows).

lobes. No pericardial or pleural effusions were seen. Apart from minimal mucosal thickening and polyp-like changes in the right maxillary sinus, there was no other pathology detected in the airways.

OUTCOME AND FOLLOW-UP

The patient was seen for a follow-up appointment 2 months after discharge. He reported complete recovery without sequelae. On discharge, he felt fatigue, which gradually subsided in the following 3–4 weeks. There were no complications during

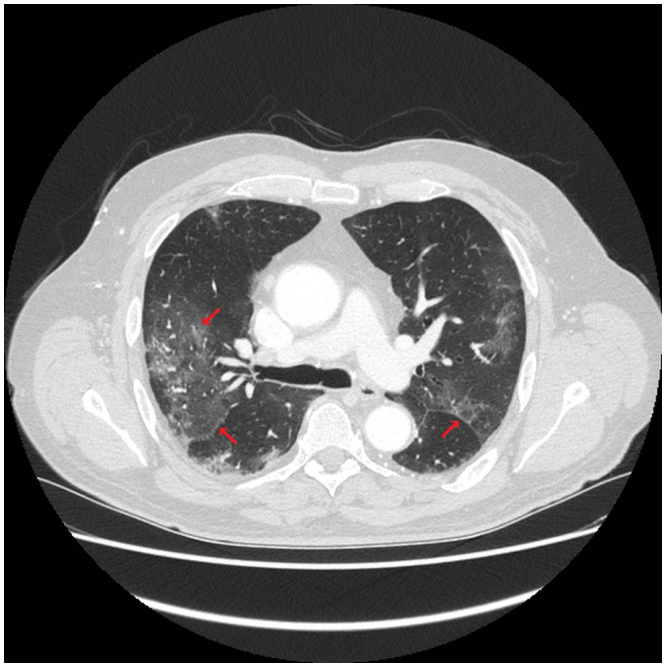

Figure 2 CT scan in axial plane showing ground glass opacities (arrows).

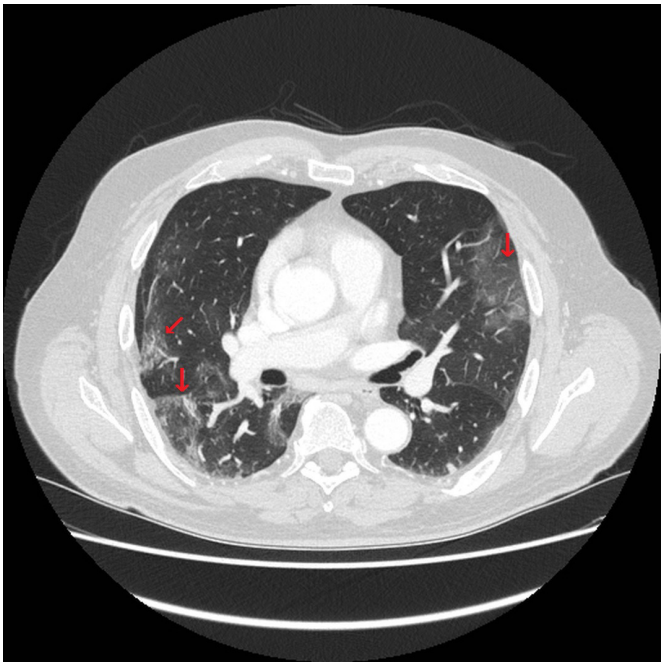

Figure 3 CT scan in axial plane showing ground glass opacities extending to the pleura (arrows).

hospitalisation. He particularly mentioned a pronounced positive effect of oxygen therapy which increased his appetite and general condition within hours. He was slowly regaining the 4 kg of weight that he had lost. CRP, alanine aminotransferase and blood monocytes had all normalised 10 weeks after initial contact. Follow-up blood tests are shown in table 2.

DISCUSSION

SARS-CoV and the Middle East respiratory syndrome coronavirus are among the previously identified human pathogenic coronaviruses. Both are known to cause respiratory and enteric illness. Gastrointestinal (GI) symptoms appear to be less common

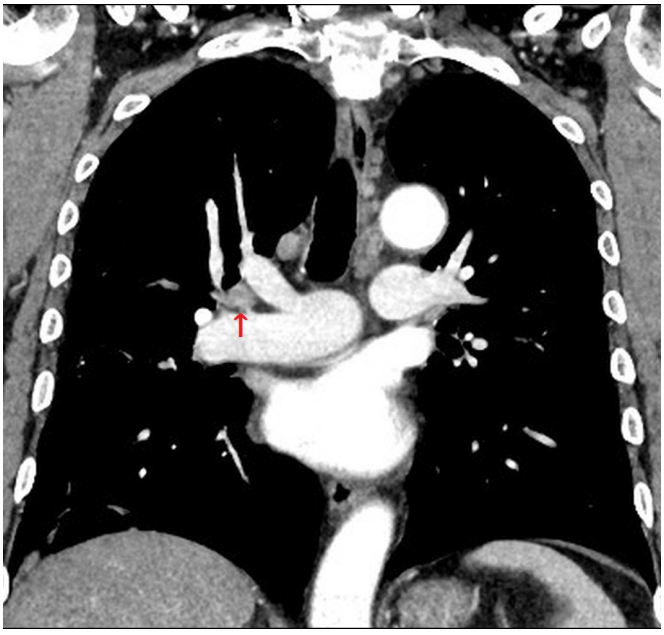

Figure 4 CT scan in coronal plane showing mediastinal lymph node enlargement (arrow).

Table 2 Biochemical profile at follow-up 10 weeks after discharge

Test	Value	Reference range
C reactive protein (mg/L)	<2	<8
Alanine aminotransferase (U/L)	22	10–70
Monocytes (×10^9/L)	0.5	0.2–0.7
Leucocytes (×10^9/L)	8	3.5–10
Neutrophils (×10^9/L)	4.4	2–7.6
Lymphocytes (×10^9/L)	3.1	1.3–3.5
Thrombocytes (×10^9/L)	235	145–350
Haemoglobin (g/L)	139	134–169
Total cholesterol (mmol/L)	3.7	<5
Triglycerides (mmol/L)	1.5	<2
Creatine kinase (U/L)	76	50–200
Low-density lipoprotein (mmol/L)	1.9	<3
High-density lipoprotein (mmol/L)	1.2	>1

in SARS-CoV-2 compared with SARS-CoV,[3] but studies are continually published. Since COVID-19 is still a novel disease, it might be too early to conclude which symptoms are typical and which are not. A recent comprehensive systematic review and meta-analysis reported a pooled prevalence of digestive symptoms of 15%. The three most common GI manifestations were loss of appetite (21%), diarrhoea (9%) and nausea or vomiting (7%).[4] While fever was the most frequent manifestation and relatively constant across the studies shown in table 3, diarrhoea ranged from 2% to 18.6%. In the meta-analysis by Mao *et al*[4], the frequency of diarrhoea ranged from 1% to 34%. It is also important to note that symptoms from different organ systems may present at different times in the course of the disease. For instance, diarrhoea and cough may occur after fever has abated.[5] These circumstances, which may complicate the diagnostic process, are important to recognise.

The cause of these different presentations is an interesting matter. Factors such as genetics, age, immunological response and viral properties could be relevant explanations. As a result of a synonymous mutation, variations in viral components responsible for antigenicity and immunogenicity were found in a recent study. This indicates the possible existence of strains with either increased or decreased virulence.[6] The founder effect must be taken into consideration, though. Further studies are needed to validate the significance of these findings and contribute to the understanding of the evolutionary trends of SARS-CoV-2. Studies of the already known coronaviruses have shown that the virions resemble a wreath or a crown due to the conformation of the surface glycoproteins. This explains the Latin name corona. In contrast to most enveloped viruses, these glycoproteins enable the virus to withstand the conditions of the GI tract and thus spread faeco-orally.[7] Xiao *et al*[8] found that 53.4% of patients had SARS-CoV-2 RNA in stool. Among these, 23% still tested positive in faecal samples after converting to negative in respiratory samples. Similar to SARS-CoV, virological studies

Table 3 Prevalence of symptoms (%)

	Fever	Dyspnoea	Sore throat	Cough	Diarrhoea	Myalgia
Zhang *et al*[21]	75.26	36.6	50.52	44	18.6	22.68
Liu *et al*[22]	81.8	19	–	48.2	8	32.1*
Xu *et al*[23]	78	–	26	63	6	28
Chen *et al*[24]	83	31	5	82	2	11

*Myalgia or fatigue.

have pointed towards the ACE2 receptor as the site of cell entry of SARS-CoV-2.[9] Previous studies have shown that ACE2 is an enzyme which physiologically counters the activity of the renin-angiotensin-aldosterone system and thus decreases blood pressure.[10] It is a membrane-bound receptor which is expressed in the vascular endothelia, cardiovascular and renal tissue, epithelium of the small GI tract, and testes. ACE2 is abundantly present in the alveolar epithelium of the lungs and the small intestinal tract including the duodenum, jejunum and ileum.[11 12]

The mechanism by which GI manifestations occur is presumably multifactorial. Positive immunofluorescent staining of ACE2 and intracellular viral capsid protein in GI tissue has been reported.[8] Combined with the presence of viral RNA in faecal samples, this suggests secretion of infectious virions in faecal matter. These findings indicate that direct virus-mediated tissue damage may be a possible pathophysiological explanation. The endothelial expression of ACE2 facilitates the involvement of vascular beds across several organs. Histopathological examination of the small intestine has shown endotheliitis of the submucosal vessels with apoptotic bodies and accumulation of inflammatory cells. This may cause endothelial dysfunction, vasoconstriction and mesenteric ischaemia.[13] Evidence of interstitial oedema with infiltration of plasma cells and lymphocytes in GI tissue has also been reported.[8] These findings contribute to the understanding of GI manifestations of COVID-19.

It is of high importance that healthcare workers are familiar with typical as well as atypical presentations and the course of this novel disease. Due to the focus on respiratory symptoms in the early stages of the pandemic, our patient was not initially suspected for COVID-19 and thus he was sent for further testing without isolation. In our case, the main suspicion was influenza disease or occult cancer. Among the different blood tests in table 1, the elevated ferritin level particularly stands out. It is known that ferritin levels may increase during inflammatory, infectious and malignant disease among others. Zhou *et al*[14] found that ferritin levels were clearly elevated in cases of COVID-19 with fatal outcome compared with survivors. Another recent study found significantly elevated ferritin levels in patients with severe COVID-19, and it was the last blood parameter to normalise. A decrease in ferritin levels was not seen along with patient improvement. Therefore, it was suggested that it is a sensitive marker of severe COVID-19, but it cannot be used for disease assessment.[15] Moreover, it has been found that elevated ferritin, erythrocyte sedimentation rate, CRP, fibrinogen and procalcitonin were higher in patients with thrombotic complications.[16] The present knowledge thus suggests that elevated ferritin level is a marker of severe COVID-19 and is associated with thrombotic complications.

After the CT scan, the main differential diagnoses were pneumonia, eosinophilic pneumonia and COVID-19. A systematic review of chest CT results in 919 patients showed that GGO was the most frequent finding and was present in 22% of the patients, while 12% had bilateral lung involvement.[17] Radiological findings of GGO have also been reported in asymptomatic patients.[18] This demonstrates the importance of guidelines being continually updated and communicated to clinicians. As already mentioned, a significant number of patients are tested positive for virus RNA in stool samples. Although it is still not clear to what extent SARS-CoV-2 spreads faeco-orally, testing of stool should be further investigated in order to optimise disease control.

As an additional note related to atypical symptoms, a recent study found that patients might present with conjunctivitis as the only symptom of COVID-19.[19] Finally, some patients experience

Patient's perspective

It all began when I came home from tennis and felt slightly cold with a mild fever. In the following days, the fever continued and fluctuated between 37.5°C and 39.2°C, and my appetite was decreasing. At first, I could not eat anything sweet. Later this came to include ordinary food as well. I developed a feeling of unease in my body, and I was prescribed paracetamol for my fever and general condition. I experienced severe sweating every time I took paracetamol. My wife is a former nurse, and we were both convinced that I was having influenza. The Danish Health Authorities had encouraged citizens to stay home in the presence of cough, fever, shortness of breath or musculoskeletal aches. Approximately a week after onset, I went to my physician, and my blood tests showed signs of mild inflammation. After three days, I came back for a check-up appointment which showed a further increase in the inflammatory count. I had no appetite and felt very ill, tired and disheartened. I experienced severe unease and slept very poorly. After a thorough examination, the doctor said, "At this time, I don't know the cause of your condition. I would like to refer you for further examination in order to rule out severe illness and malignant disease and to find the underlying cause." I was given an appointment the following day for further blood tests and imaging. The imaging of my lungs showed signs of possible coronavirus infection, and I was admitted to hospital in isolation. I was tested with a throat swab, and some fluid was obtained from my airways through a tube in my nasal cavity. I was then discharged and told that we would be informed about the test results. Late in the evening close to midnight, we were contacted with the results. I had coronavirus. Half an hour later an ambulance arrived, and I was admitted to an isolated COVID-19 unit at another hospital nearby. Further tests were conducted, and I was given nasal oxygen therapy because of a low oxygen level in my blood. Shortly after, I felt significantly better. The only therapy I received during my eight days at the hospital was oxygen therapy. For every day that passed, I felt better, and my appetite returned. When I was discharged, I was told that I had to be symptom-free for at least 48 hours before I could consider myself recovered. Did I have any remnants of the disease? I was very tired, but this receded in the following three to four weeks. While I am writing this, it has been seven weeks since I was discharged. I have recovered completely, and my condition is now as good as it was before I fell sick with coronavirus. I now play tennis three times a week again, and I am looking forward to the reopening of the gym. Throughout my illness, I have received fantastic treatment by all parts of the health care service, and I am deeply grateful.

Learning points

- Our understanding of typical and atypical symptoms of COVID-19 is still under development.
- The existing evidence suggests that gastrointestinal manifestations are present.
- This calls for increased focus on atypical non-respiratory symptoms of COVID-19 for optimal disease control.
- It is important to recognise typical as well as atypical presentations of COVID-19 in general practice and other places with initial contact.

olfactory and gustatory disturbances such as hyposmia, anosmia and dysgeusia in the absence of other symptoms.[20]

Acknowledgements Maria Tudborg was actively involved in clinical decision making as senior consultant in general practice.

Contributors SFW was the lead author of the manuscript and was involved in initial care and management, case identification, manuscript write-up and drafting, editing and literature review. BBL was senior supervisor and was involved in acquisition of data and imaging and performed critical revision and editing of the manuscript for important intellectual content. SFW and BBL were equally involved in the design and interpretation of data.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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