Internal and Emergency Medicine (2020) 15:1587–1589
https://doi.org/10.1007/s11739-020-02453-6

CE - LETTER TO THE EDITOR

Should the search for COVID-19 become part of the work-up of incidental thromboembolism? A near-missed COVID-19 diagnosis

Marta Franceschini[1] · Massimiliano Carlin[1] · Massimo Porta[1] · Maria Felice Brizzi[1,2]

Received: 23 June 2020 / Accepted: 15 July 2020 / Published online: 24 July 2020

Dear Editor,

The COVID-19 pandemic outbreak has raised novel medical challenges and several unsolved issues. The present case draws attention to two major problems: clotting alterations in the SARS-CoV-2 infection and the reliability of currently available diagnostic tests.

At the end of February 2020, returning from a trip to his native Burkina Faso (01/2020), a 64 year old man started to suffer from moderate fatigue, not impacting on daily life, and abdominal discomfort. He denied fever, cough, dyspnoea, diarrhoea or contacts with known cases of COVID-19 over the previous 3 months. History was unremarkable, except for poorly controlled type-2 diabetes on metformin (HbA1c 74 mmol/mol, 8.9%) and a 1 cm liver mass, previously identified as a lipoma and on radiological follow-up.

After a negative first level work-up, the General Practitioner requested a contrast-enhanced abdominal Computerized Tomography (CT), which showed no changes of the liver mass. However, as the upper scans revealed subsegmental embolism of the lower left lung, the patient was referred to the Emergency Department.

On admission, pulse was 90 bpm regular, blood pressure 165/90 mmHg, respiration rate 20 per minute, and body temperature 36 °C. The patient was eupnoeic at rest with oxygen saturation 96% breathing ambient air. Physical examination only unrevealed bilateral basal crackles. First-line laboratory findings showed normal full blood count (FBC), renal and liver function, and increased D-Dimer (2022 µg/ml, n.v. < 500 µg/ml) (Table 1). A chest CT-scan identified sub-segmental thrombosis in the apical segment of the left inferior lobe and the lateral sub-segment of the right medium lobe. It also showed diffuse sub pleural ground-glass interstitial involvement, especially in the areas, where thrombosis was detected (Fig. 1). Low molecular weight heparin (LMWH) was started at anti-coagulant dosage.

According to the local COVID-19 protocol the following procedures were performed:

- 6-min Walking Test (6-MWT), showing desaturation (89%, > 4% from rest);
- Nasopharyngeal (NF) swab: negative for the presence of COVID-19.

Despite the negative swab result, the CT-scan and 6-MWT findings led us to consider the patient as highly suspicious for SARS-CoV-2 infection. According to the diagnostic algorithm of the Italian Society of Emergency Medicine (SIMEU) the patient was classified at low mortality risk and admitted to the COVID-19 "grey-line" low intensity unit for such cases.

The patient was subjected to droplet and contact isolation and, 24 h later, a second NF-swab was again negative. To further rule out SARS-CoV-2 infection, a bronchoalveolar lavage was performed, which also turned negative for SARS-CoV-2, A/B influenza and respiratory syncytial viruses.

An Eco Doppler scan of the lower limbs did not reveal deep vein thrombosis. Therefore, potential prothrombotic conditions were considered:

- Abdomen and chest CTs were negative for solid neoplasms and venous thrombosis;
- Prostatic Serum Antigen levels were normal;
- FBC was normal;
- Screening for thrombophilia revealed normal levels of C protein, S protein, activated protein-C resistance, antiphospholipid antibodies (lupus anti-coagulant anti-

Marta Franceschini and Massimiliano Carlin contributed equally.

✉ Maria Felice Brizzi
mariafelice.brizzi@unito.it

[1] Department of Medical Sciences, University of Turin, Corso Dogliotti 14, 10126 Turin, Italy

[2] Azienda Ospedaliera Universitaria Città della Salute e della Scienza, Turin, Italy

Table 1 Patient 's biochemical data on admission

WBC $*10^9$ /L	6.10
LNF$*10^6$ /L (%)	1750 (28.7%)
N 10^6 /L (%)	3810 (62.5%)
RBC* 10^{12} /L	4.84
Hb g/dl	15.3
PLTS 10^9 /L	248
CRP mg/L	1.5
Pct ng/mL	0.04
INR	1.04
aPTT ratio	0.88
AST UI/L	12
ALT UI/L	11
Bilirubin mg/dL	0.6
D-Dimer ng/mL	2022
Fibrinogen mg/dL	360
Glucose mg/dL	252
Creatinine mg/dL	0.75
Urea mg/dL	21
CK UI/L	74
LDH UI/L	397
NT-proBNP pg/mL	154
T-troponin ng/L	6
Pancreatic Amilase UI/L	9
Na^+ mmol/L	138
K^+ mmol/L	4.5

WBC white blood cells, *LNF* lymphocytes, *N* neutrophils, *RBC* red blood cells, *Hb* hemoglobin, *PLTS* platelets, *CPR* C-reactive protein, *PCT* procalcitonin, *INR* International normalized ratio, *aPTT ratio* activated partial thromplastin time ratio, *AST* aspartate transaminase, *ALT* alanine transaminase, *CK* creatin kinase, *LDH* lactate dehydrogenase, *NT-Pro-BNP* N-terminal fragment-prohormone brain natriuretic peptide

cardiolipin and ß2-microglobulin), factor V Leiden, and factor II variants;

- Serum protein electrophoresis showed a non-specific γ globulin increase.
- Then, 2 days before dismissal, a qualitative assay revealed the presence of SARS-CoV-2 IgG in the serum, suggesting COVID-19.

The patient was discharged at home with a diagnosis of SARS-CoV-2 related interstitial pneumonia and sub-segmental pulmonary thromboembolism with a prescription for direct oral anticoagulants and no specific therapy for SARS-CoV-2.

Two discrete COVID-19-associated clotting alterations are known: low grade disseminated intravascular coagulation and thrombotic microangiopathy, especially localized to the lung [1]. These abnormalities have been linked to increased circulating levels of pro-inflammatory cytokines (particularly IL-1, TNF-α and IL-6) and endothelial damage. Clinically, the most relevant alterations associated with clotting abnormalities in COVID-19 patients are mild thrombocytopenia, prolongation of the PT segment, and increased D-Dimer, which is considered an important negative prognostic factor. Zhou et al. [2] reported an 18-fold higher risk of death in patients with D-Dimer greater than 1000 µg/ml on admission and Thachil et al. [3] suggested hospitalization for all patients with D-Dimer 3–4 times over the normal range, even in the absence of severe symptoms. In our patient, the most likely mechanism supporting sub-segmental thromboembolism was SARS-CoV-2 -related thrombotic microangiopathy.

This leads to a number of questions. Should the differential diagnosis of otherwise, unexplained incidental thromboembolism include the active search for SARS-CoV-2 infection? Should we continue searching for markers of infection even in patients with thrombosis without clear SARS-CoV-2 associated clinical symptoms or pulmonary signature? Will testing for SARS-CoV-2 infection become part of routine screening for prothrombotic conditions even after the current pandemic era will be hopefully over?

The latter question leads to the second issue: how to detect the infection? Currently, physicians face two hurdles: asymptomatic patients who elude controls, remaining a reservoir for infection, and symptomatic ones in whom search for the virus is persistently negative. We know very little about the sensitivity and specificity of available diagnostic tests and even less about their clinical relevance. In addition, their reliability depends on operator accuracy and time of sampling. For example, NF-swabs are reported to turn positive 7–10 days after the onset of symptoms, while bronchoalveolar lavage (BAL) does so after 3 weeks. In addition, although RT-PCR is widely used to identify COVID-19 patients, no viral load threshold has been correlated to infectiousness [4]. NF-swab and BAL false negatives are a commonly experience and represent a problem for clinicians [5]

This report suggests that, in suspicious cases, clinical judgment based upon biochemical and radiological findings remains a cornerstone in the diagnosis of SARS-CoV-2 infection. However, since infections and, in general, inflammatory diseases are well-known triggers of thrombosis, in the presence of typical laboratory or radiologic findings such as ground-glass lesions at CT-scan, SARS-CoV-2 infection should be carefully ruled out.

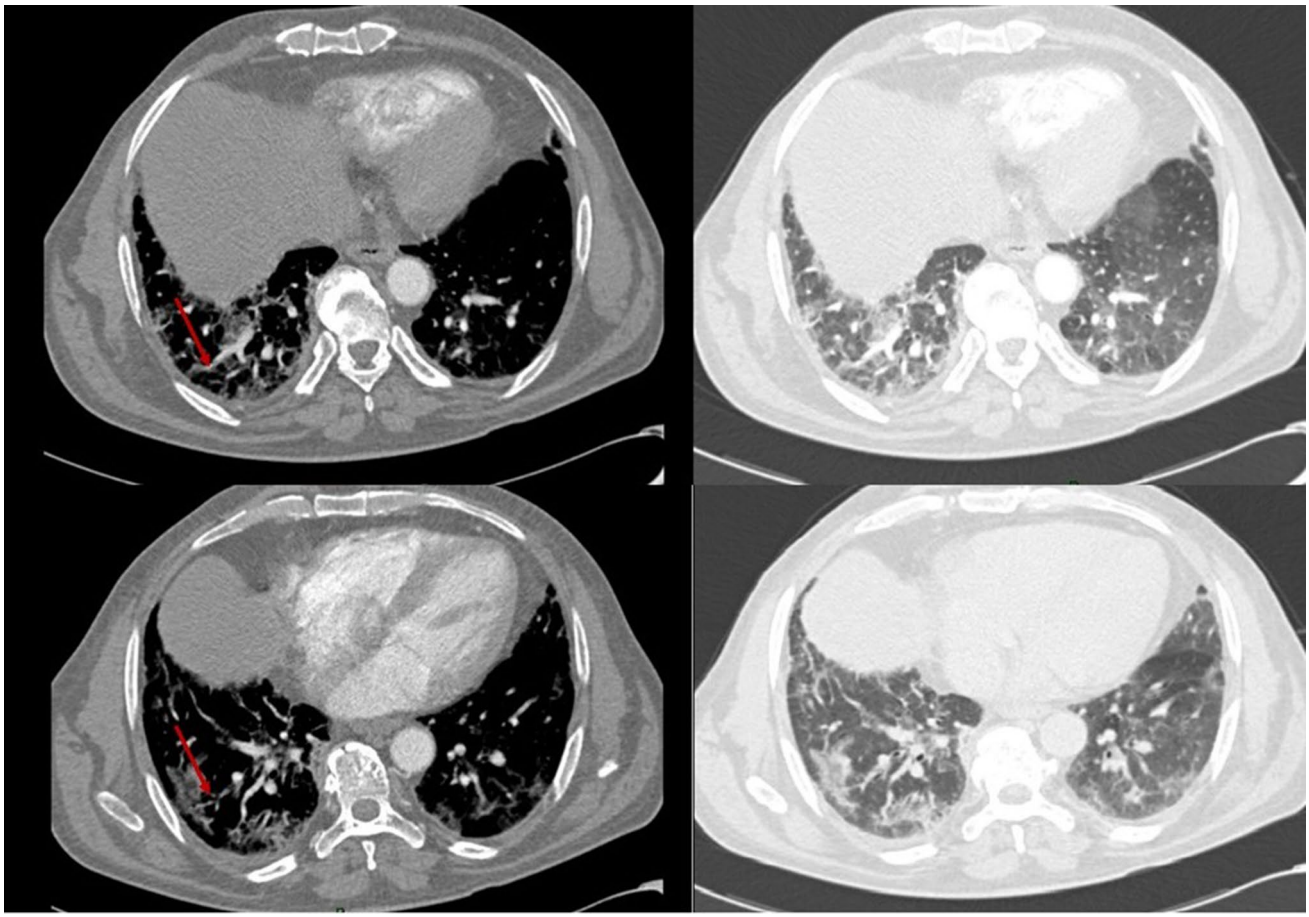

Fig. 1 Patient's chest CT-scans. The left scans show sub-segmental thromboembolism (red arrows), localized in inferior right lobe (upper scan) and medium right lobe (lower scan). The right scans show the ground-glass opacities localized in the same areas

Compliance with ethical standards

Conflict of interests The authors have no competing interest to declare.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Levi M, Thachil J, Iba T, Levy JH (2020) Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 7(6):e438–e440. https://doi.org/10.1016/S2352-3026(20)30145-9
2. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. Lancet 395(10229):1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3**(2020 Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]**)
3. Thachil J, Tang N, Gando S et al (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 18(5):1023–1026. https://doi.org/10.1111/jth.14810
4. Loeffelholz MJ, Tang YW (2020) Laboratory diagnosis of emerging human coronavirus infections: the state of the art. Emerg Microbes Infect 9(1):747–756. https://doi.org/10.1080/22221751.2020.1745095
5. Woloshin S, Neeraj Patel MD, Aaron BA, Kesselheim S (2020) False negative tests for SARS-CoV-2 infection: challenges and Implications. New Engl J Med. https://doi.org/10.1056/NEJMp2015897