

# Iliopsoas hematoma in patients with COVID-19 on low-molecular-weight heparin treatment

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## Abstract

Patients with COVID-19 are at high risk of thromboembolic events; for this reason, the use of heparin is largely recommended but, in addition to thrombotic complications, bleeding is a significant cause of morbidity in patients with COVID-19. Idiopathic iliopsoas hematoma is a very rarely described hemorrhagic complication in patients with COVID-19. We report here two cases of iliopsoas hematoma in male patients with COVID-19 and being treated with heparin.

## Keywords

Iliopsoas hematoma, COVID-19, low-molecular-weight heparin

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## Introduction

There are increasing reports in the literature of high rates of coagulopathy and venous thromboembolism (VTE) among hospitalized patients with coronavirus disease 2019 (COVID-19).<sup>1–5</sup> For this reason, the WHO has also recommended the use of heparin, preferably low-molecular-weight heparin (LMWH) for the prevention of thromboembolism in COVID-19 patients.<sup>6</sup> Heparin, in addition to its function of anticoagulant, has also probably got an anti-inflammatory action through various mechanisms, such as the inhibition of the synthesis of thrombin, the link with inflammatory cytokines, the inhibition of neutrophilic chemotaxis and leukocyte migration, and the neutralization of the C5a peptide.<sup>7–9</sup> Heparin may also have an antiviral role: its molecules possibly bind to circulating coronaviruses, thus not allowing their binding to the heparan-sulfate proteoglycans present on the surface of the cells, and thus effectively preventing the penetration of the virus into the cell.<sup>10</sup> Several studies have evidenced how major hemorrhages represent an uncommon, but dramatic, complication of COVID-19 infection.<sup>11–13</sup> Although age, anticoagulation, a high body mass index and dialysis seem to be risk factors for developing an iliopsoas hematoma (IPH) in patients with compromised clinical conditions,<sup>14</sup> idiopathic IPH was reported very rarely as a hemorrhagic complication in patients with COVID-19.<sup>15,16</sup> In a

3-month period (March–May 2020), we treated 78 COVID-19 patients with LMWH prophylaxis. We had four bleeding episodes: two cases of minor hematuria related to catheter insertion and two cases of idiopathic IPH. We report these two cases of association with IPH and COVID-19.

## Case report

### Case 1

The first patient, a male, aged 75 years, affected by chronic obstructive pulmonary disease, was being treated with clopidogrel due to carotid atheromatous plaques and a previous ischemic stroke. In March 2020, because of a rapidly

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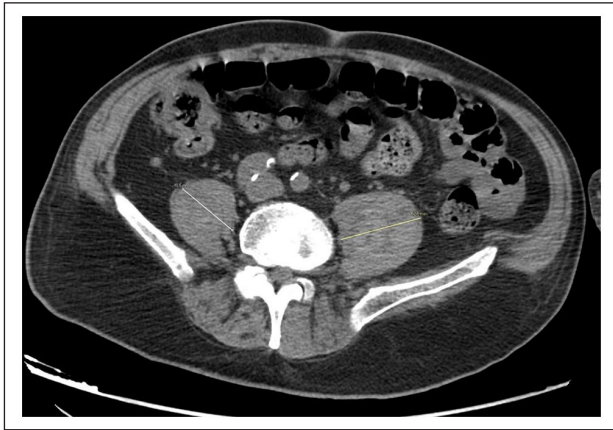
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**Figure 1.** CT total body. Evidence of bilateral iliopsoas muscle volume increase, with different levels of attenuation from hemorrhagic infarction.

worsening pneumonia, and after a sudden loss of consciousness, he underwent a nasal swab test which revealed COVID-19 infection. He received treatment with lopinavir/ritonavir and hydroxychloroquine. According to the local hospital guidelines about high prophylactic heparin dosage in COVID-19 patients, the antiplatelet agent was suspended and treatment with enoxaparin 4000 IU twice daily was started. Seven days after hospitalization, the patient had a transient ischemic attack: for this reason, it was decided to increase the LMWH dosage to 6000 IU twice daily. After 10 days, the patient developed abdominal pain: therefore, a computed tomography (CT) scan was performed, which revealed evident thickening with signs of hyperemia and oedematous imbibition, in both iliopsoas muscles, with hematoma axial dimensions of 40.5 mm on the left and 52.6 mm on the right (Figure 1). The hemoglobin (HB) values decreased ( $-2$  g/dL). No variation of coagulation parameters such as prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen was detected before, during and after the onset of this hemorrhagic event; we only observed a moderate thrombocytopenia ( $81 \mu\text{L}$ ) 2 days before the onset of the hematoma, then the platelet count returned to a normal level after 4 days. D-Dimers (normal values  $0-0.55$  microg/mL), which had a mean value of 3.46 (range =  $0.95-9.27$ ) in the admission period before the IPH, after this diagnosis showed a decrease: mean 0.4 (range =  $0.25-0.53$ ). Because of the high risk of thromboembolism due to COVID-19 and to the patient's clinical conditions, we decided not to stop LMWH but to reduce the dosage to 4000 IU twice daily. The patient underwent blood transfusions and after stabilization of HB parameters, the enoxaparin dosage was increased to 5000 IU twice daily, with the purpose of better preventing venous and arterial thrombosis. The hematoma was completely reabsorbed after 27 days. The patient was discharged after 49 days of hospitalization, enoxaparin 5000 IU twice daily was prescribed to



**Figure 2.** CT total body. Hematic infarction of the right iliopsoas muscle.

be continued for a further month, after which the clopidogrel therapy would be resumed.

### Case 2

A 79-year-old male with fever, cough, and dyspnoea was hospitalized for respiratory failure associated with a positive COVID-19 nasal swab sample. At the time of admission, symptoms had manifested 10 days earlier; he suffered from hypertension and was not on any antithrombotic treatment before hospitalization. After admission, he was put on therapy with Baricitinib and hydroxychloroquine. He also started increased LMWH dosage prophylaxis with enoxaparin 6000 IU twice daily. The decision to start with a higher dosage was taken because the patient was obese, weighing 93 kg, and following our local COVID-19 guidelines about increased dosage of heparin in overweight patients. Two weeks after admission, the patient showed an unprovoked right IPH (Figure 2). Due to the hematoma onset, enoxaparin was reduced to 5000 IU twice daily. No changes were observed in the PT, PTT, fibrinogen coagulation parameters, nor a reduction in the platelet count. The mean D-Dimer value of the period before the diagnosis of IPH was 0.73 (range =  $0.26-1.33$ ); after the onset of IPH, there was a mean value of 0.94 (range =  $0.43-1.40$ ). The hematoma was completely reabsorbed after 21 days. The patient was discharged after 57 days of hospitalization, with an indication to continue heparin therapy for 1 month after discharge.

### Discussion

The low incidence of serious bleeding events (2/78 2.5%) and thrombosis (1/78 1.3%) in our COVID-19 patients treated with LMWH leads us to conclude that, similarly to what has been reported by other authors, the prophylaxis with increased heparin dosage can be considered effective and safe. The onset of hematoma of the IPH, which constituted 50% of the cases of all reported bleeding events in our

experience, and the fact that these were without an apparent cause, led us to believe that hospitalized COVID-19 patients may be considered, for still unknown reasons, at risk of IPH. It would have been very useful to measure the anti-factor Xa activity, in order to highlight a possible overdose of LMWH, but unfortunately this was not viable due to the impossibility of carrying out such specific tests in our laboratory during the first wave of COVID-19 in Italy. We observed a non-homogeneous trend of D-Dimers in these two patients: this was probably due to the different course of the disease, and the related contemporaneous causes of increase and decrease, including the inflammation caused by COVID-19 infection, the previous cerebral ischemia occurred before IPH in the first patient, and the fact that both patients were on LMWH therapy before and during the IPH. In our cases, monitoring the D-Dimer levels did not contribute to preventing the bleedings. There are currently two reports describing cases of IPH in COVID-19 patients. In the first report, Patel et al.<sup>15</sup> described a 69-year-old male taking aspirin because a past medical history of coronary artery disease (CAD), hypertension and type 2 diabetes mellitus, who was given daily 4000 IU subcutaneous prophylactic enoxaparin after hospitalization, and who developed severe IPH after 20 days; unfortunately, the article does not report the data of the coagulation parameters, but only the normal platelet count. In the second report, Mazzitelli et al.<sup>16</sup> described two cases: a 74-year-old man treated with LMWH at a dosage of 4000 IU twice a day for atrial fibrillation (AF) who died of severe anemia resulting from IPH, with a worsening prolongation of PT and PTT during hospitalization, and a 56-year-old man with stroke and renal failure also treated with LMWH 4000 twice a day for AF, with a normal coagulation pattern at the time of admission, and onset of IPH after 27 days: at the time of the diagnosis of hemorrhage, only PT was moderately increased and an unspecified thrombocytopenia was noted. There are also other reports in the literature concerning idiopathic IPH in anticoagulated patients even if not affected by COVID-19: Apostolopoulos et al.<sup>17</sup> described a man treated with warfarin who developed extensive IPH with femoral nerve palsy. A similar case is reported by Watanabe et al.<sup>18</sup> where a patient, also on warfarin treatment, developed a rhabdomyolysis caused by bilateral IPH. Risch et al.<sup>19</sup> described five cases of non-traumatic IPH in patients treated with an anticoagulant. Since IPH is a serious bleeding complication, treatment with anticoagulants must be suspended in order not to aggravate the bleeding and put the patients' life at risk. Instead, we decided to reduce LMWH therapy but not to suspend it, because of the very high risk of thromboembolic complications, as described by the first reports and case series in COVID-19 patients. A clear example of a high thrombotic risk was the onset of cerebral ischemia in the first patient, despite the heparin therapy at a dosage of 4000 IU b.i.d. For the above reasons, the continuation of the anticoagulant treatment in both patients was preferable, even after the diagnosis of IPH, while monitoring the progressive

reduction until complete re-absorption of the hematoma, through frequent hemoglobin assessments, as well as radiological examinations. Patients with COVID-19 and under LMWH prophylaxis should be carefully monitored with the aim to identify early clinical signs related to IPH, and then should undergo radiological exams as soon as possible, especially in cases where there is a reduction in hemoglobin levels and a worsening of clinical conditions during treatment of COVID-19, not otherwise explainable.

## Conclusion

Differently from what has been observed by other authors in COVID-19 reports, in which changes in coagulation correlated with bleeding risk have been reported, in our experience the absence of coagulation alterations and the fact that only one of the two patients had moderate and transient thrombocytopenia seems to confirm that IPH cannot be directly related with any certainty to depletion of coagulation factors or consumption of platelets. Further studies are needed to assess the hemorrhagic risk of antithrombotic therapy, as well as investigation of pre-existing coagulation defects or those caused by the infection, which may predispose COVID-19 patients to bleeding.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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## Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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