

Lesson by SARS-Cov 2 disease (COVID-19): whole body CT angiography detection of relevant and other/incidental systemic vascular findings

Gaetano Rea

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Francesco Lassandro

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Roberta Lieto (✉ roblieto@gmail.com)

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Giorgio Bocchini

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Federica Romano

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Giacomo Sica

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Tullio Valente

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Emanuele Muto

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Patrizia Murino

ICU, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Antonio Pinto

Department of Radiology, Azienda dei Colli, CTO Hospital, Naples, Italy

Vincenzo Montesarchio

Division of Medical Oncology, AORN Azienda dei Colli, Monaldi Hospital, Naples, Italy

Maurizio Muto

Department of Radiology, Azienda dei Colli, Monaldi Hospital, Naples, Italy

Daniela Pacella

Department of Public Health, University of Naples Federico II, Naples, Italy

Ludovica Capitelli

Respiratory Medicine Unit, Department of Clinical Medicine and Surgery, Federico II University of Naples, Italy

Marialuisa Bocchino

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Abstract

Objectives: The aim of our study was to assess the frequency distribution of relevant and incidental vascular events in a retrospective cohort of 42 COVID-19 patients.

Methods: All patients were studied by whole-body CT angiography.

Twenty-three out of 42 patients were admitted to the intensive care unit (ICU).

Results: Relevant vascular events were recorded in the 71.4% of the whole study population. Pulmonary embolism was the most frequent one both in ICU and no-ICU cases (56.5% vs10.5%, $p=0.002$). Ischemic infarction of other organs was affecting with an increasing prevalence the gut, the spleen, the liver, the brain and the kidney, with a simultaneous ischemic occurrence in some cases. Multi-focal venous thrombosis was also represented especially in ICU patients ($p=0.005$). Among incidental findings, splanchnic vessels little-size aneurysms were reported in the 40% of the whole population, with relative frequencies similarly distributed in ICU and no-ICU patients.

Conclusions: Vascular involvement is not negligible in COVID-19 and should be carefully investigated as may significantly affect disease behavior and prognosis.

Key Points

Coronavirus disease (COVID-19) affects all human organs, with a peculiar tropism for the vasculature due to the wide expression of angiotensin-converting enzyme-2 receptors.

Pulmonary embolism was the most frequent relevant vascular event both in ICU and no-ICU cases.

Among incidental findings, splanchnic vessels little-size aneurysms were reported in the 40% of the whole population.

Introduction

The rapid worldwide infection spreading of the emergent coronavirus SARS Cov-2 and of its related disease termed COVID-19 have dramatically challenged the medical community. This because of the unexpectedly high degree of aggression of possible clinical scenarios, with the lung being the most frequently affected site [1-3]. Manifestations of COVID-19 range from asymptomatic infection and mild upper respiratory illness to severe bilateral pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure and death [4-6]. Since the first cases of SARS Cov-2 related pneumonias were reported in Wuhan, China, [1-3], growing literature evidence clearly suggests that COVID-19 is a systemic disease as it may affect almost all the human organs. In this issue, both venous and arterial thrombosis events have been reported as main complications of COVID-19 in intensive care unit (ICU) patients likely due to the uncontrolled cytokine storm that occurs in severely ill cases [7, 8]. Pulmonary embolism (PE) first, and then deep vein thrombosis (DVT), systemic arterial embolism, myocardial infarction and ischemic stroke

are among the most frequently encountered manifestations that contribute to increase morbidity and mortality [7-14]. Given these observations, we aimed to assess the frequency distribution of systemic vascular events recorded by means of whole-body (WB) CT angiography in a retrospective COVID-19 patient cohort admitted to our hospital because of SARS Cov-2 related pneumonia between March 16th and April 30th. Extra-vascular findings were recorded as well.

Materials And Methods

All contrast-enhanced WB-CT angiography scans performed in our center between March 16th and April 30th in patients tested positive for SARS Cov-2 by means of reverse-transcriptase chain reaction on nasopharyngeal swabs were retrospectively obtained from the Picture Archiving and Communication System (PACS). WB-CT angiography was performed as follows. Briefly, baseline brain and lung volumes were acquired before the double-phase high speed injection of the contrast medium (arterial and venous phase acquisition) that allowed the further sampling of the brain, neck, chest, abdomen, and pelvis. Data acquisition was performed with a 128-MDCT Ingenuity scanner (Philips Healthcare) and a 64-MDCT Light Speed VCT scanner (GE Healthcare) with the following parameters: 120 kVp; 100-200 mAs; pitch: 0.75-1.5; and collimation: 0.625-1.25 mm. Images were reconstructed with a slice thickness of 1-1.25 mm using a high sharp reconstruction algorithm (bone filter for lung evaluation). A dedicated soft-tissue filter was used for the evaluation of the neck, abdomen, and pelvis; the same was performed for the brain study. WB-CT images were acquired with the patient in the supine position. For the lung study, full inspiration was required when feasible. All WB-CT angiography studies were independently and blindly reviewed by four radiologists with 8-20 years of experience. Thorax imaging was analyzed with both the lung (width: 1500 HU; level: -700 HU) and mediastinal (width: 350 HU; level: 40 HU) setting. A dedicated reconstruction filter was adopted for the study of the extra-thoracic organs. Multi-planar reconstruction (MPR) was used to resolve any interpretation doubt.

According to Thompson RJ *et al.*, findings were classified as: "*relevant*", that is related to the chief complaint, strictly pertinent to the immediate patient care and management; or "*other/incidental*", which are findings unrelated to the chief complaint and not pertinent to the immediate patient care [15].

The study was approved by the local institutional Ethics Committee (protocol n. 0021131/2020) and conducted according to the principles of the Declaration of Helsinki. Informed consent was waived due to its retrospective nature and emergency setting.

Statistical analysis

Numerical variables were described using the mean \pm standard deviation (SD) in case of symmetrical distribution or the median with interquartile range [25th; 75th percentile] in case of variables showing consistent skewness. Categorical variables were summarized using absolute frequencies and percentages. The Student T Test, the Mann Whitney U test or the Fisher exact test were used for

comparisons among study groups, where appropriate. All tests were two-tailed. A p value <0.05 was considered significant.

Results

During the study period, 42 out of 126 hospitalized patients underwent contrast enhanced WB-CT angiography, including 23 cases admitted to ICU. Main clinical indications in no-ICU patients included acute onset or unexplained worsening of dyspnea, sudden onset of edema of the limbs, and acute alterations of consciousness. Worsening hypoxemia and D-Dimer increase (>2 fold) were the main hallmarks in ICU cases. Demographics and clinical features of the study population are reported in Table 1. As shown, there were no significant differences related to gender and age between ICU and no-ICU patients, while the frequency of active smokers was higher in the former. Also, the prevalence of patients with comorbidities, like type II diabetes, was significantly higher among ICU cases, most of them being also obese. Systemic hypertension was similarly distributed in the two study groups, while no patients had any underlying chronic lung disease. SARS Cov-2 related pneumonia was detected in all of them with an estimated mean CT disease extent of 13.7 according to the lung severity score by Zhao W *et al.* [16]. Lung involvement was significantly greater in ICU patients, all of them requiring mechanical ventilation, as compared to no-ICU cases (16 ± 3.2 vs 11 ± 4.1 , $p<0.0001$). Figure 1 shows a representative bilateral pneumonia with ARDS-like features in an ICU patient. All patients were under anti-viral therapy with lopinavir/ritonavir.

The frequency distribution of relevant vascular-related events detected by means of WB-CT angiography are depicted in Table 2A. Overall, they were reported in the 71.4% (n=30) of the study population, with a prevalence of 91% (n=21) and 47% (n=9) in ICU and no-ICU patients, respectively. Relevant vascular-related findings included both thrombotic/thromboembolic and hemorrhagic events. Pulmonary thromboembolism was the most frequent one in the whole population (35.7%), occurring in more than half of the ICU patients, being associated with local or multi-focal detectable lung infarcts in the 19% of cases. A representative example of massive PE occurring in a previously healthy young patient with no known risk factors is reported in Figure 2. Ischemic infarction of other organs was affecting with an increasing prevalence the gut, the spleen, the liver, the brain and the kidney, with a simultaneous ischemic occurrence in some patients, as shown in Figure 3 in a representative case. Multi-focal venous thrombosis was also highly represented both in the superior and inferior vena cava districts, again with the majority of cases being distributed among ICU patients. Finally, active bleeding, likely including both spontaneous and iatrogenic events, was recorded in a minority of patients with the involvement of skeletal muscles in the 11.9% of cases. A representative patient with multi-focal hemorrhages is shown in Figure 4.

Other/incidental vascular-related findings are reported in Table 2B. They included portal vein enlargement and splanchnic vessels little-size aneurysms (40% of the whole population), with relative frequencies similarly distributed in ICU and no-ICU patients. The enlargement of the main pulmonary artery was also evident in both study sub-groups.

The most prevalent relevant extra-vascular related findings are summarized in Table 3A. Pneumothorax and pneumomediastinum accounted for the 14% of events, with no differences among ICU and no-ICU cases. Acute pancreatitis was detected in 3 ICU patients with no relation to previous chronic alcohol consumption or to gallbladder or biliary tract diseases. According to the revised Atlanta classification [17], pancreatitis was mild in 2 cases and moderate-to-severe in the other one.

Other/incidental extra-vascular related findings included a wide array of alterations depicted in Table 3B. Overall, there were no significant differences between ICU and no-ICU patients. The most prevalent findings were hepatomegaly, ascites and splenomegaly with a decreasing frequency ranging from 28.5% to 16.6%.

Six ICU patients died accounting for an overall mortality rate of 26%.

Discussion

To the best of our knowledge, this is the first report addressing the prevalence distribution of systemic vascular alterations evaluated by means of whole-body CT angiography in a retrospective cohort of 42 patients admitted to our hospital between March and April 2020 due to SARS-Cov-2 related pneumonia. Since the first description in last December of COVID-19 cases in Wuhan, China, it is emerged that the lung is the main target organ of this novel coronavirus that infects alveolar cells through the angiotensin-converting enzyme 2 (ACE2) receptor [1-3, 18]. COVID-19 pneumonia has been largely studied with a significant proportion of patients all over the world with severe organ impairment requiring mechanical ventilation. These efforts have provided a detailed record of differential CT patterns, that range from focal ground-glass opacities through acute respiratory distress syndrome-like pictures [19], along with the publication of a multinational consensus statement from the Fleischner Society focused on the management of this topic [20]. Apart from the lung parenchyma, the pulmonary vasculature is also involved, being the most frequently affected site in the case of thrombotic alterations. The last ones seem to be related to the so-called cytokine storm that results from viral infection in more severe COVID-19 patients [21, 22]. In the dramatic scenario of the emerging SARS-Cov-2 pandemic where the whole medical community was found disoriented, radiology has played a pivotal role in the diagnostic work-up as in the clinical decision-making process. This because radiology has brought out that COVID-19 is a multi-organ disease most insidious than initially was thought, with vascular involvement accounting for increased morbidity and mortality. The case series we describe herein is the first one focused on the systemic evaluation of the vascular compartment in a selected cohort of COVID-19 patients we observed very early during the pandemic spreading in our geographical area in a time period when treatment strategies were not yet efficiently tailored. Vascular CT findings were recorded both in ICU and no-ICU patients and were differentiated into either clinically relevant or incidental. Certainly, they were most frequently represented in ICU patients, in whom more advanced lung disease along with comorbidities, obesity and increased IL-6 levels were likely to play as triggering factors. In agreement with previous observations, pulmonary embolism was overall the most frequent event (35.7% of the total patient population), with the 86% of cases in ICU patients, none of them with a previous history of deep vein

thrombosis or PE. Venous thrombosis occurred in different sites and accounted for the 26% of total clinically relevant events with the 62.5% of cases admitted to ICU. Additional vascular events widely ranged from pulmonary infarction and ischemic brain injury to infarction of abdominal parenchymal organs with a similar frequency distribution between ICU and no-ICU patients which was suggestive of a sort of dysregulation of the coagulation process even in less severe patients. This finding is in agreement with data by Santoliquido *et al.* who reported a 11.9% incidence of deep vein thrombosis in a cohort of 84 no-ICU COVID-19 patients receiving thromboprophylaxis [23]. Altogether, these observations are of utmost clinical relevance as anticoagulation therapy has been shown to significantly improve patient outcome when started early, instead of sole prophylaxis, at least in moderate-high risk patients [24-27]. Incidental vascular findings were also similarly distributed in both ICU and no-ICU cases, with aneurysms of the splanchnic vasculature being present in the 30% of ICU patients.

When looking at extra-vascular findings, clinical events included ventilation-related complications like pneumothorax and pneumomediastinum only in a small proportion of ICU cases. Acute pancreatitis, that Aloysius *et al.* have reported as COVID-19 presenting event [28], was also detected in 3 ICU cases thus allowing clinicians to start targeted therapies.

Our study has some limitations that first include the small sample size and its retrospective nature. Certainly, despite a not negligible rate of deaths (26%), our observations have been helpful to our clinicians as ameliorated patient management and therapy in their daily practice reinforcing the role that a multi-disciplinary team may have in a critical setting like this. Results of statistical tests should be interpreted with caution as not significant p values do not necessarily rule out any difference between ICU and no-ICU patients. Also, the study time period was very short and limited to the very early disease occurrence. Comparison with a larger cohort including COVID-19 patients receiving tailored treatments (i.e., anti-coagulation drugs, systemic corticosteroids) should have been useful to address how the *disease appearance* has changed over time along with the improvement of medical interventions. According to literature data, the prevalence of thrombotic events in ICU patients can be up to 60%, with incidental thrombo-embolic alterations being detected by CT in the 31.9% of ICU cases [29, 30]. This means that it is not possible to exclude that the high frequency of such alterations in our ICU COVID-19 case series was independent on the SARS Cov-2 infection but related to ICU hospitalization itself. Again, comparison with no COVID-19 ICU patients should have been interesting but unfortunately not reliable because of the emergency working conditions. Despite this, the high prevalence of ACE2 receptors in the vascular compartment along with the clinical observation that COVID-19 patients experienced a sudden deterioration of their conditions short after hospitalization strongly suggest a close causative link with the dysregulation of the host immune response driven by the viral infection.

In conclusion, this is the first report addressing the prevalence distribution of systemic vascular events in COVID-19 patients presenting with moderate-to-severe pneumonia and evaluated by WB-CT angiography. Vascular involvement is not negligible in these patients reflecting the disease aggressiveness and failure of initial treatment strategies mainly based on anti-viral and weak anti-inflammatory drugs (i.e., hydroxychloroquine or clarithromycin).

Declarations

Conflict of interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Abbreviations

ICU: intensive care unit

PE: Pulmonary embolism

DVT: deep vein thrombosis

WB-CT: whole body computed tomography

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Tables

Table 1. Demographics and clinical features of the study population

Parameter	ICU patients (n=23)	No-ICU patients (n=19)	p
Age (yrs)	58±12	64±14	0.163
Gender, M (%)	16 (69)	14 (74)	1.000
Smoking (%)	11 (48)	2 (10)	0.017
Type II diabetes (%)	19 (83)	5 (26)	<0.001
Systemic hypertension (%)	8 (35)	5 (26)	0.739
Obesity (%)	11 (48)	2 (10)	0.017
D-dimer (ng/ml)	570 [368-2908]	690 [336-1402]	0.940
C reactive protein (mg/dl)	17 [11.5-28.8]	15 [7.4-22.3]	0.172
Ferritin (ng/ml)	1052 [527-1212]	718 [478-1211]	0.312
Interleukin-6 (ng/ml)	356 [41-763]	45 [33-64]	0.003
Blood lymphocytes/mm ³	800 [600-1100]	870 [720-1410]	0.456
Endotracheal intubation	23 (100)	0 (0)	<0.001
Non invasive ventilation	0 (0)	8 (44)	0.001
LMW prophylaxis (%)	23 (100)	8 (44)	<0.001
Death (%)	6 (26)	0 (0)	0.024

Data are expressed as mean±SD or as median [25th-75th], where appropriate. Statistically significant results are reported in bold.

Table 2. Frequency distribution of *relevant* (A) and *other/incidental* (B) findings of vascular-related events by contrast-enhanced whole body CT angiography

A)

Parameter	Total patients (n=42)	ICU patients (n=23)	No-ICU patients (n=19)	p
Ischemic brain injury	6 (14.2%)	4 (17.4%)	2 (10.5%)	0.672
Pulmonary thrombo-embolism	15 (35.7%)	13 (56.5%)	2 (10.5%)	0.003
Pulmonary infarction	8 (19%)	5 (21.7%)	3 (15.7%)	0.709
Venous thrombosis (jugular/subclavian/axillary/superior vena cava)	11 (26%)	10 (43.4%)	1 (5.2%)	0.005
Aorta thrombosis	1 (2.3%)	1 (4.3%)	0	1
Internal carotid artery thrombosis	2 (4.7%)	2 (8.7%)	0	0.492
Hepatic infarction	2 (4.7%)	2 (8.7%)	0	0.492
Splenic infarction	3 (7.1%)	1 (4.3%)	2 (10.5%)	0.581
Renal infarction	8 (19%)	6 (26%)	2 (10.5%)	1
Mesenteric ischemia	1 (2.3%)	1 (4.3%)	0	0.258
Ileopsoas hematoma with active bleeding	4 (9.5%)	2 (8.7%)	2 (10.5%)	1
Rectus abdominis/quadriceps femoris hematoma with active bleeding	1 (2.3%)	1 (4.3%)	0	1
Ileo-femoral vein thrombosis	2 (4.7%)	2 (8.7%)	0	0.492

B)

Parameter	Total patients (n=42)	ICU patients (n=23)	No-ICU patients (n=19)	p
Main pulmonary artery enlargement (>30 mm)	2 (4.7%)	2 (8.7%)	2 (10.5%)	1
Portal vein enlargement (>16 mm)	8 (19%)	4 (17.4%)	4 (21%)	1
Splanchnic vessels aneurysm	9 (21.4%)	7 (30%)	2 (10.5%)	0.149

Data are reported as absolute number (%). Statistically significant results are reported in bold.

Table 3. Frequency distribution of *relevant* (A) and *other/incidental* (B) findings of extra-vascular related events by contrast-enhanced whole body CT angiography

A)

Parameter	Total patients (n=42)	ICU patients (n=23)	No-ICU patients (n=19)	p
Pneumothorax	3 (7.1%)	2 (8.7%)	1 (5.2%)	1
Pneumomediastinum	3 (7.1%)	3 (13%)	0	0.238
Acute pancreatitis	3 (7.1%)	3 (13%)	0	0.238

B)

Parameter	Total patients (n=42)	ICU patients (n=23)	No-ICU patients (n=19)	p
Cervical subcutaneous emphysema	3 (7.1%)	3 (13%)	0	0.238
Hydropericardium	2 (4.7%)	2 (8.7%)	0	0.492
Pneumoretroperitoneum	2 (4.7%)	2 (8.7%)	0	0.492
Mediastinal lymphadenopathy	2 (4.7%)	1 (4.3%)	1 (5.2%)	1
Ascites	11 (26%)	9 (39%)	2 (10.5%)	0.075
Hepatomegaly	12 (28.5%)	8 (34.7%)	4 (21%)	0.494
Splenomegaly (>15 cm)	7 (16.6%)	5 (21.7%)	2 (10.5%)	0.427
Hydropic gallbladder	1 (2.3%)	1 (4.3%)	0	1

Data are reported as absolute number (%).

Figures

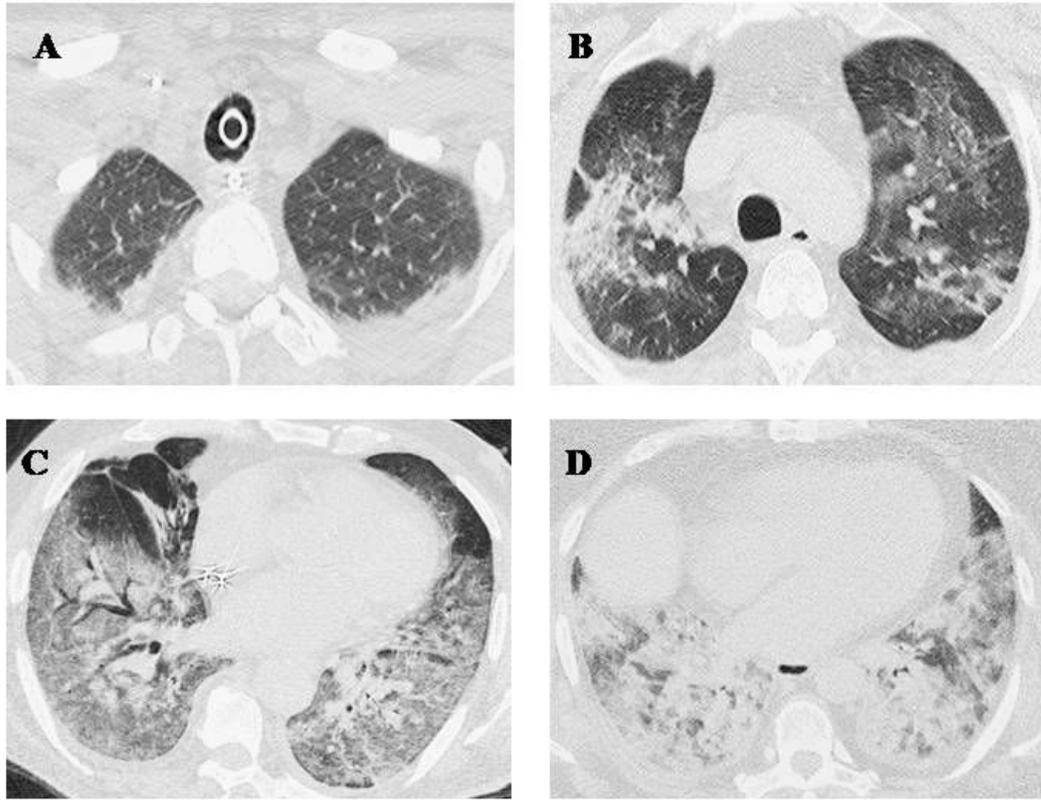


Figure 1.

Figure 1

Axial thin-section baseline un-enhanced lung CT scan in a 33-yr old man who presented with fever and cough ultimately requiring ICU admission due to significant worsening of respiratory failure. Diffuse bilateral confluent and patchy ground-glass and consolidative pulmonary opacities are evident from the lung apices (A-B) to the bases (C-D), with a total severity score of 20/24 (see text).

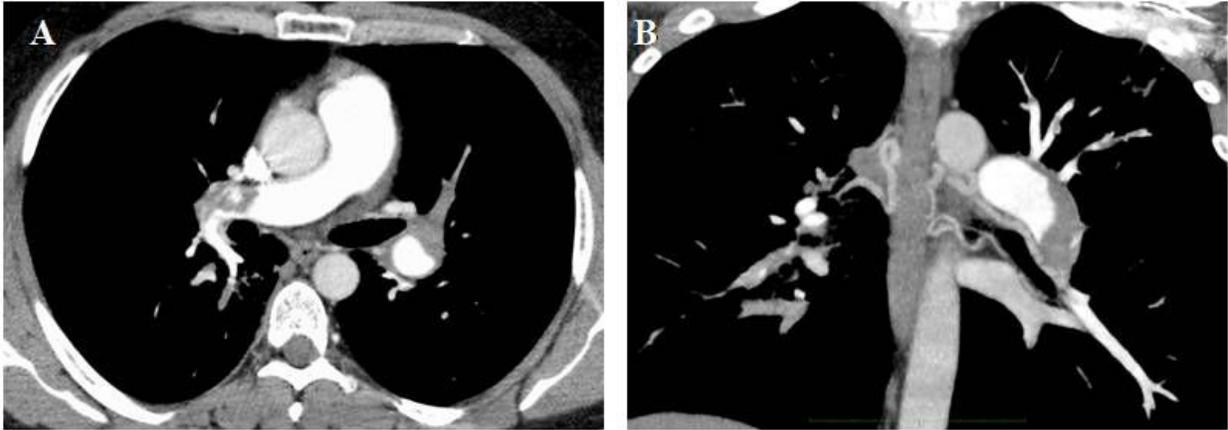


Figure 2.

Figure 2

Contrast-enhanced lung CT angiography in a 33-yr old man (same case of Figure 1) showing the presence of extensive emboli obstruction of the right main branch of the pulmonary artery (A) and extensive emboli obstruction of the left main branch of the pulmonary artery and bronchial artery ectasia (MPR - B).

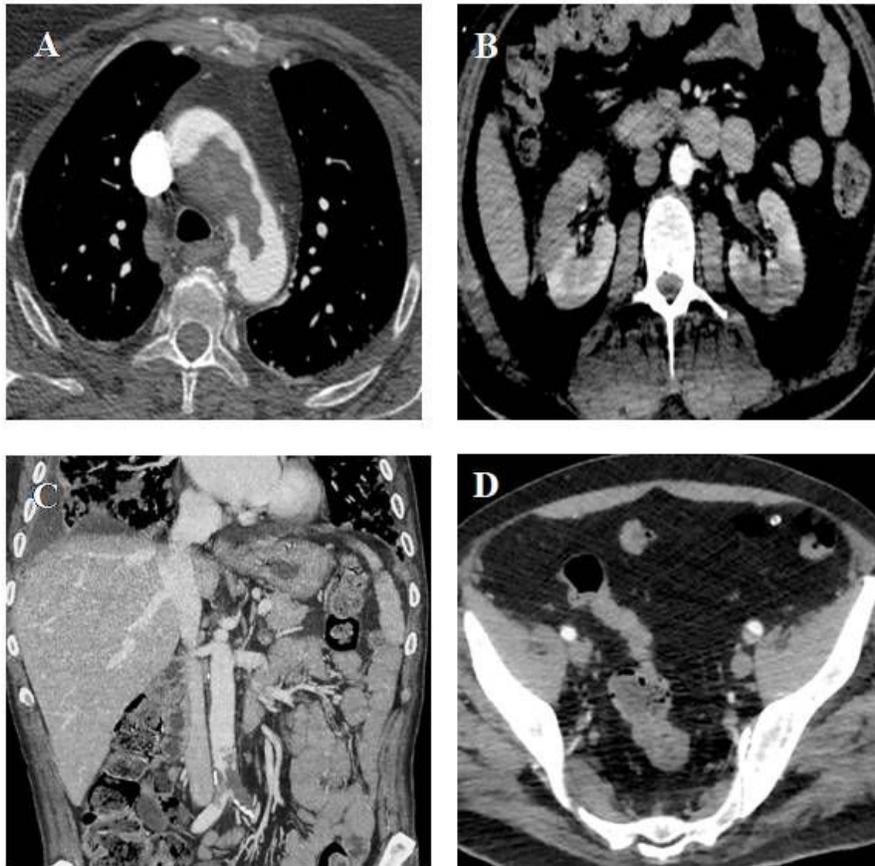


Figure 3.

Figure 3

Medium enhanced CT angiography showing an extensive thrombotic filling defect within the aortic arch (A) and bilateral kidney infarction (B) in a 57-yr old no-ICU patient with acute chest pain and sudden onset of discoloration of the upper limbs. Thrombosis of the distal aorta and iliac artery (C) along with the concomitance of left iliac artery partial thrombotic occlusion in a 68-yr old ICU patient with acute onset of lower limbs edema (D).

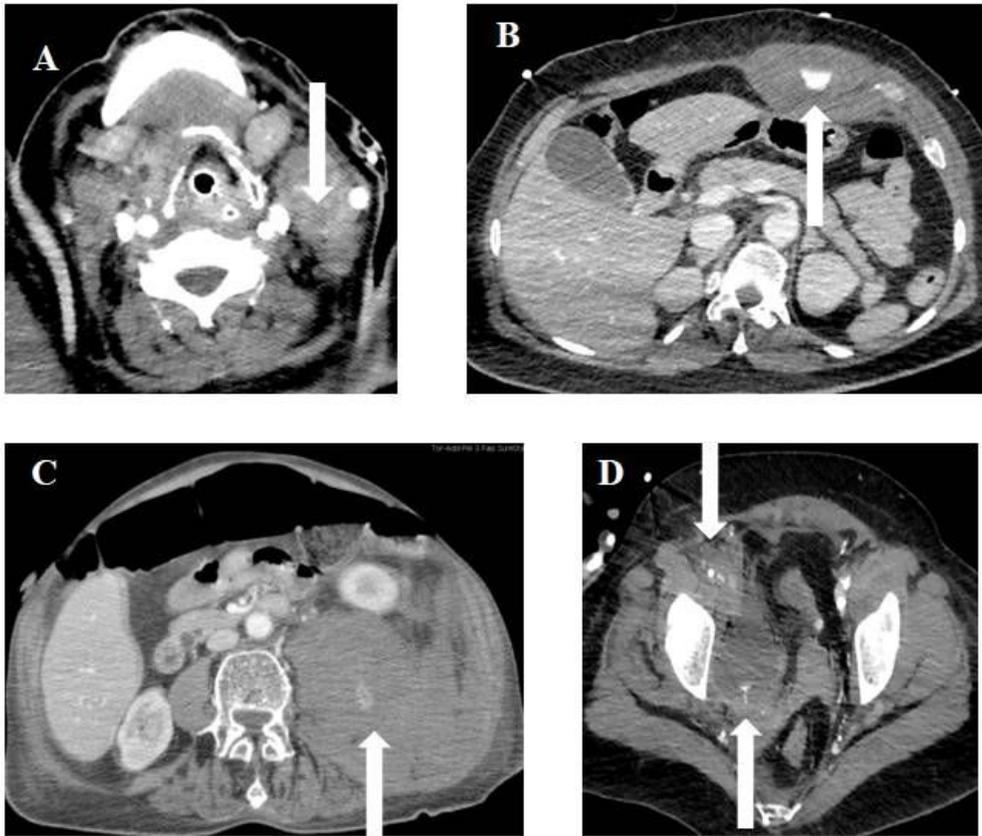


Figure 4.

Figure 4

Multisite active bleeding in a 63 yr-old ICU patient with sudden onset of dyspnoea along with acute severe anemia. Arrows show contrast medium extra-vasation in the left carotid space (A), in the left rectus abdominis muscle (B), in the left psoas muscle and homolateral perirenal/posterior pararenal space (C) and in the right iliac extra-peritoneal space (D).