Disseminated intravascular coagulation: A devastating systemic disorder of special concern with COVID-19

Parmvir Singh | Robert A. Schwartz

Dermatology, Rutgers-New Jersey Medical School, Newark, New Jersey

Correspondence
Robert A. Schwartz, Dermatology, Rutgers University New Jersey Medical School, Medical Science Building H-576, 185 South Orange Avenue, Rutgers-New Jersey Medical School, Newark, NJ 07103.
Email: roschwar@cal.berkeley.edu

Abstract
Disseminated intravascular coagulation (DIC) is linked with severe COVID-19, prompting considerable concern. DIC can be a devastating systemic disorder. It is often markedly manifest on the skin as acrocyanosis or as petechiae and purpura with progression to hemorrhagic bullae. Subcutaneous hematomas may occur, as may thrombotic findings including necrosis and gangrene. The most common cause is infection, with special emphasis now on COVID-19. We have reviewed the medical literature under the search terms “Disseminated intravascular coagulation” and “consumption coagulopathy” for the past two decades in the English language using Medline and Google Scholar to update special concerns and considerations, focusing on those with COVID-19. Skin findings with DIC may be prominent. The severity of cutaneous lesions often correlates with the gravity of systemic disease. DIC is most effectively treated by addressing the underlying cause and resuscitating the patient using supportive measures. It is pivotal to recognize and treat DIC early, before deadly complications, such as multiple organ failure, arise.

KEYWORDS
bullae, COVID-19, disseminated intravascular coagulation, petechiae, purpura fulminans, sepsis, skin

1 | INTRODUCTION

Disseminated intravascular coagulopathy (DIC) is linked with severe COVID-19, as are other COVID-19-associated coagulopathies.1 Disseminated intravascular coagulation (DIC) is a clinically striking condition of inflammatory, systemic hemostasis first reported by Dupuy in 1834.1-3 This activation overcomes anti-coagulation mechanisms, leading to fibrin clot formation within small and medium sized vessels.1,2,4 The pathogenesis involves endothelial injury, exposing sub-endothelial collagen, so that microthrombi are formed as the underlying pathology.5,6 Hemostasis, along with inflammation, may lead to organ failure, particularly in those that are critically ill.1,7 Depletion of coagulation factors leads to risk of serious hemorrhagic complications.1,2 DIC may be caused by malignancy, infection, hypoxia, hypoxemia, trauma, burns, vascular disorders, immunologic disorders, toxins, hepatic disease or peripartum complications.1,2,5,8-13 DIC may occur with metastatic cutaneous melanoma.2 Acute myeloid leukemia and prostate cancer are the most common causative malignancies.8 The severity of skin findings in DIC has not been classified. The development of DIC in patients with COVID-19 unfavorably alters its clinical course.3 Routine monitoring of hemostasis tests is important in selected COVID-19 patients.

2 | CUTANEOUS MANIFESTATIONS

Clinical patterns with DIC are varied, exemplified by those identified with COVID-19, from petechial to acro-ischemia presentations including finger/toe cyanosis, skin bulla and dry gangrene, some resembling chilblains disease (Figures 1 and 2).7 Hypercoagulable states in DIC are associated with a set of common cutaneous manifestations.14 In a

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A study of 36 patients with DIC, cutaneous findings were the presenting sign in 47% of them. They were caused by either initial thrombosis or hemorrhage secondary to consumption of coagulation factors. Skin manifestations caused by hemorrhage occurred with the following frequencies: petechiae (61%), purpura (83%), palpable purpura (32%), hemorrhagic bullae (19%), subcutaneous dissecting hematomas (31%), or bleeding from wound/IV sites (39%). Skin manifestations caused by thrombosis included acral cyanosis (25%) and gangrene (17%). Purpura fulminans is a combination of hemorrhagic and thrombotic findings.

In DIC, petechiae are miniscule, pin-point sized, macules caused by hemorrhage from skin capillaries. They are sometimes papular, palpable petechiae (Figures 1 and 2). Purpura is evident as non-blanching, erythematous macules, patches, or plaques varying in size from 5 to 20 mm. They may be flat or raised, palpable purpura with clear or necrotic centers. Purpura and petechiae become palpable due to increased hemorrhage and edema. Purpura is similar to petechiae, but larger and in this setting often has sharply demarcated borders. Petechiae and purpura are usually limited to the extremities. They have a propensity to occur in wounds and at pressure points. The purpura may become large and widespread enough to converge and develop into hemorrhagic bullae (Figure 3). When of less than 24 hours duration, petechiae and purpura are characterized by thrombi in the superficial vascular plexus at the junction of the papillary and reticular dermis. Older lesions contain epidermal necrosis, subepidermal bullae, and glandular necrosis. Other hypercoagulable states that cause purpura include thrombotic thrombocytopenic purpura, warfarin skin necrosis, heparin-induced thrombocytopenia, calciphylaxis, and catastrophic antiphospholipid syndrome. Palpable purpura may be caused by septic emboli, allergic cutaneous vasculitis, drug reaction (penicillin, sulfonamides), or systemic necrotizing angitis. Palpable purpura is the hallmark of leukocytoclastic vasculitis. Hemorrhagic bullae are filled with blood. Large hemorrhagic bullae may undergo necrosis and gangrenous change and require distinction from erythema multiforme or bullous pemphigoid. Bullae in DIC must also be differentiated from Steven-Johnson syndrome, the flaccid bullae in toxic epidermal necrolysis (TEN) and dissecting hematomas, which are extensive subcutaneous accumulations of blood that are rapidly progressive and painful.

DIC may also be evident with cyanosis, which appears as a non-blanching, central gray patch surrounded by irregular, erythematous or purplish borders. It is most commonly located on the digits, but may also be found on the ears and nose. Acral cyanosis may evolve into gangrene. Indwelling arterial and venous catheters are associated
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with an enhanced risk of acral cyanosis and gangrene. Acral cyanosis must be distinguished from Raynaud’s phenomenon, chilblains, and acrocyanosis.8

It is important to differentiate the thrombotic/coagulopathic vasculopathic acral ischemia as seen in DIC from chilblain-like lesions (blue “COVID toes”), also associated with the COVID-19 pandemic.4 This acral ischemia due to thrombosis in COVID-19 patients with severe disease reflects a hypercoagulable state and highly elevated D-dimer levels. Unlike the other skin findings in COVID-19, chilblain-like lesions are unassociated with severe disease but may represent a clue to COVID-19 diagnosis.20 They clinically and histologically strongly resemble idiopathic and autoimmune related chilblains.21 There are no data to our knowledge to support that acral ischemia as seen in DIC and chilblain-like findings are different degrees of involvement within the same spectrum.7,8,20

Gangrene of hands, feet, tip of the nose, ear, and posterior scalp may occur in DIC.15 Symmetrical peripheral gangrene (SPG) is gangrene of the acral parts of the body. The hypercoagulable state of DIC results in microvascular occlusion beginning distally and advancing proximally.22 SPG manifests as fever, followed by cyanosis, pallor, and pain, and is often caused by Gram-positive and Gram-negative organisms, rarely caused by tuberculosis.23,24 There is an association between cold ambient temperature and the development of gangrene, postulated to be related to increased vasospasm.25 SPG is almost universally associated with DIC. Gangrene has been found to have a mortality of 35%.23-25 Gangrene may lead to osteomyelitis.15 In one study of 12 patients, 3 died within 1 week and 8 of the remaining 9 required amputation.24 There is also some risk of auto-amputation of digits.8

Purpura fulminans, the most fatal presentation of DIC, is a dermatologic emergency.14 It manifests as multiple purple/erythematous, nonblanching, confluent macules, hemorrhagic bullae, and skin necrosis.5,14 Purpura fulminans is rapid in onset and extensive.5,8,12 Late findings in purpura fulminans include geographic plaques, hemorrhagic bullae, gangrene and firm eschars.12,26,27 The distal extremities are most commonly involved, but any part of the body is susceptible.5,23 It is associated with high mortality due involvement of visceral organs.5,9,28 Multiple organ failure makes DIC difficult to distinguish from TEN.19,20 Other causes of purpura fulminans include congenital protein C or S deficiency, sepsis, trauma, malignancy, obstetric complications, hepatic failure, toxins, or immunologic reactions.14

DIC may manifest at varying degrees of severity. One study found that 58% of patients presented with petechiae, 31% with purpura, 19% with palpable petechiae or purpura, 11% with acral cyanosis.8 19% of purpura progressed to hemorrhagic bullae. Two patients progressed to purpura fulminans. Palpable purpura was usually found in association with N. meningitidis infection. The combination of septic shock, palpable purpura, and acral cyanosis is very suggestive of DIC.

### 3 | ETIOLOGY

Sepsis, particularly bacterial sepsis, is the condition most commonly associated with DIC (Table 1).4 More than half of COVID-19 pneumonias admitted to intensive care at a large Texas hospital developed clinically significant thromboses that were associated with hypercoagulable thromboelastographic parameters alone.1 In fact, 30-50% of patients with gram-negative sepsis have DIC, but it is just as common in those with gram-positive sepsis.4-29 Systemic coagulation is activated by lipopolysaccharide, endotoxin, or exotoxin.4 Trauma, particularly brain trauma, results in DIC by the release of fats and phospholipids, hemolysis, and endothelial damage.4 Both solid and hematologic malignancies cause DIC due to expression of tissue factor on tumor cells.3,30 Obstetrical complications, such as placental abruption and amniotic fluid embolism, cause a self-limited DIC due to leakage of a thromboplastin-like substance.4-31

| TABLE 1 | Common etiologies of disseminated intravascular coagulopathy |
|----------|-------------------------------------------------------------|
| **Type** | **Cause**                                                        |
| Infection | Bacterial (gram-negative sepsis, gram-positive sepsis)  |
|           | Rickettsiosis (rocky mountain spotted fever, scrub typhus) |
|           | Viral (HIV, CMV, HSV, rotavirus, influenza, varicella-zoster virus, Ebola, dengue, COVID-19) |
| Fungal    | (histoplasmosis, candida sepsis, aspergillosis, Candida auris) |
| Malignancy | Hematological malignancy (acute promyelocytic leukemia, acute lymphoblastic leukemia) |
|           | Solid tumor (prostate carcinoma, gastric carcinoma, pancreatic carcinoma, colon carcinoma, breast carcinoma) |
|           | Metastases                                                    |
| Obstetrical complications | Abruptio placenta |
|                      | Pre-eclampsia                                                   |
|                      | Eclampsia                                                      |
|                      | Acute fatty liver of pregnancy                                  |
|                      | Amniotic fluid embolism                                        |
|                      | Septic abortion                                                 |
|                      | Intrauterine fetal demise                                      |
| Coagulation disorders | Protein C deficiency                                          |
|                      | Antithrombin III deficiency                                    |
| Other                | Hypoxia                                                        |
|                      | Hypoxemia                                                      |
|                      | Liver disease/hepatic failure                                  |
|                      | Toxins (viper venom, insect bites)                             |
|                      | Pancreatitis                                                   |
|                      | Giant hemangiomia                                              |
|                      | Severe inflammatory bowel disease                              |

Abbreviations: CMV, cytomegalovirus; COVID-19, Coronavirus-2019; HIV, human immunodeficiency virus; HSV, human herpes virus.
Diagnostic criteria for disseminated intravascular coagulation from three different organizations

| Table 2 | Diagnostic criteria for disseminated intravascular coagulation from three different organizations |
|---------|------------------------------------------------------------------------------------------------|
| **International Society on Thrombosis and Hemostasis** | **Japanese Association of Acute Medicine** | **Japanese Ministry of Health and Welfare** |
| **Underlying disease** | 0 points, but patient must have an underlying disorder known to be associated with DIC | 1 point | 0 points, but patient must have an underlying disorder known to be associated with DIC |
| **Clinical symptoms** | 0 points | Bleeding: 1 point Organ failure: 1 point | SIRS score ≥ 3: 1 point |
| **Platelet count (x10^3/μL)** | >100—0 points <100 but >50—1 point <50—2 points | >120—0 points <120 but >80—1 point <80 but >50—2 points <50—3 points | <120 but >80 or >30% drop—1 point <80 or >50% drop—3 points |
| **Fibrin-related marker** | Elevated fibrin monomers/degradation products: No increase: 0 Moderate increase: 2 Strong increase: 3 | Fibrin degradation products μg/mL >10 but <20—1 point >20 but <40—2 points >40—3 points | Fibrin degradation products μg/mL >10 but <25—1 point >25—3 points |
| **Prothrombin time (PT)** | Prothrombin time: <3 seconds—0 >3 but <6—1 >6 seconds—2 | PT ratio: >1.25 but <1.67—1 point >1.67—2 points | PT ratio: >1.2—1 point |
| **Fibrinogen (g/L)** | >1 g: 0 <1 g: 1 | >1 but <1.5—1 point <1—2 points | None |

hemorrhage into the dermis, resulting information of ecchymoses, which can eventually lead to hemorrhagic bullae. Necrosis and gangrene occur when obstruction of venules distal to the dermocutaneous loop results in coagulative necrosis. Rotational thromboelastometry may be of value in reflecting a hypocoagulable or hypercoagulable profile to help delineate DIC. The prothrombin time (PT) is prolonged in DIC.9 Due to its standardization, many centers are beginning to use INR instead of PT time. An abnormal PT or aPTT is found in most patients with DIC. The differential for an elevated PT includes hepatic failure, blood loss, and vitamin K deficiency. The differential diagnosis for an elevated aPTT includes hepatic failure, blood loss, and heparin therapy. The levels of factor 8 are increased in DIC because it, along with von Willebrand factor, is released from injured vascular endothelial cells.1,6 Measurement of fibrinogen level has no proven utility in the diagnosis of DIC.1,35 Fibrin degradation products are increased in DIC.1,8,9 They are elevated in 40% of critically ill patients, 80% of trauma patients,
and nearly 100% of DIC patients.\textsuperscript{1,36} As such, the specificity of fibrin split products is not high. The differential includes hematoma, post-op status, systemic inflammation, deep vein thrombosis, and pulmonary embolism.\textsuperscript{1} Inhibitors of coagulation, such as protein C, protein S, and anti-thrombin, are decreased in 90% of patients with DIC.\textsuperscript{1} The reason for their decrease is consumption, decreased production, and increased processing by neutrophil elastase.\textsuperscript{1,37} Other causes include hepatic failure and capillary leakage.\textsuperscript{1}

The International Society on Thrombosis and Hemostasis has created a composite scoring system to assess the likelihood of coagulopathy.\textsuperscript{38} This scoring system is based on platelet count, PT, d-dimer, and fibrinogen levels. If the score is greater than or equal to 5 out of 8, then it is considered compatible with overt DIC. Other scoring systems that rely on INR instead of PT are pending widespread validation. The higher the composite score, the lower the survival rates.\textsuperscript{1} The scoring should be repeated daily if it is greater than or equal to 5.\textsuperscript{38} Prolonged elevation of PT and platelets has been associated with poorer outcomes.\textsuperscript{1,39} A gold standard does not exist for the ideal diagnostic criteria, but three are primarily used throughout the world.\textsuperscript{38,40,41}

Patients with DIC can show signs of organ failure.\textsuperscript{8,9} Blood cultures may show growth of a causative organism, such as Staphylococcus aureus, especially its community acquired methicillin-resistant form, Group A streptococci, Neisseria meningitidis, Vibrio species, or Varicella virus.\textsuperscript{5,8,11,13,15,28,42} One study reported N. meningitidis as the most common causative organism.\textsuperscript{8} If other laboratory tests are equivocal, a punch biopsy specimen of cutaneous lesions may reveal fibrin thrombi.\textsuperscript{8,9}

5 | TREATMENT

Treatment of DIC usually requires a multidisciplinary approach in an intensive care unit.\textsuperscript{24} Therapy of DIC is not directed at the skin, but rather at the management of the causative condition.\textsuperscript{1,24,42-46} COVID-19-associated DIC therapy should follow accepted strategy employing thromboembolic prophylaxis for critically ill hospitalized patients and standard supportive care measures.\textsuperscript{47} However, a lack of thrombocytopenia may mean that COVID-19 DIC is not always a typical consumptive coagulopathy with additional strategies possibly necessary.\textsuperscript{45} Transfusion of platelets, plasma, cryoprecipitate or fibrinogen concentrate should be considered for hemorrhaging patients.\textsuperscript{1,5,11,43}

Patients with DIC due to infection should have it treated, depending on the causative organism.\textsuperscript{15} Leukopenia is a poor prognostic factor.\textsuperscript{21} Resection of necrotic tissue, including escharotomies, may be required.\textsuperscript{26} Skin grafting should be performed, if possible.\textsuperscript{5,28} Amputation of gangrenous areas may be compulsory.\textsuperscript{5,8,15} While patients are being optimized for treatment, padding or vascular boots may be applied to the affected parts.\textsuperscript{21} Improvement of the dermatologic findings is a useful measure in determining response to therapy.\textsuperscript{9} With COVID-19 producing florid DIC in some hospitalized patients and acral cyanosis in a variety of settings, DIC has risen to the forefront with no clear therapy yet of proven value for the COVID-19 itself.\textsuperscript{1,4,5,7,48} Preliminary data suggests that low-dose dexamethasone may reduce deaths in hospitalized COVID-19 patients on ventilation, although its effects on DIC in this setting are yet to be determined.\textsuperscript{49} One must also watch for co-infections, as the COVID-19 pandemic may merge with the Candida auris global epidemic in the intensive care unit with DIC being produced by either and possibly both of them.\textsuperscript{50}

CONFLICT OF INTEREST

The authors have no conflicts of interest.

ORCID

Robert A. Schwartz \(\text{https://orcid.org/0000-0003-3036-3825}\)

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