Untangling Covid-19 Pathophysiology Part I: Oligomeric (Soluble) Fibrin Forming Transient Microclots Enhances the Lethality of Covid-19

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Article

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Abstract

We propose that in severely ill patients the SARS-CoV-2 virus expropriates an anomalous variant of clotting. This clotting variant produces a “bloodstream blizzard” of short-chain, soluble, fibrin molecules. If clotting continues, additional polymerization occurs and the molecular chains lengthen. With this lengthening fibrin becomes insoluble and microclots form. These microclots transiently or permanently occlude arterioles, venules and capillaries in widely separated regions throughout the body. The tissue supplied by these vessels dies. A 5-7 fold increase in circulating oligomeric fibrin typically presents about a week into severe Covid-19 pneumonia. If such patients are not immediately anticoagulated, whole body defibrination and death is the likely result.

Introduction

How is it possible for a *respiratory* virus to damage heart, liver, kidneys, and brain, precipitate diarrhea and produce skin lesions that look like frostbite? In newspaper accounts, Covid-19 has been associated with each of these findings.[1] In the formal scientific literature it is reported that this virus can damage the hematologic, cardiovascular, renal, gastrointestinal, hepatobiliary, endocrinological, dermatological, neurological and ophthalmic organ systems.[2]

Pathophysiology

No coherent explanation for these protean manifestations is on offer; that is, no encompassing pathophysiology for this disorder has been advanced that accounts for such widespread damaging effects. We propose that, in severely ill patients, Covid-19 produces these diverse, malign outcomes by partial expropriation of the clotting cascade. Other than the signs and symptoms of a viral pneumonitis, we believe that it is this expropriation of clotting and the sequelae caused by this anomalous sort of clotting that accounts for almost all of the findings in Covid-19 that are unexpected in a straightforward viral pneumonitis. In corroboration of this proposed mechanism, heparin administration, which has become routine over the last few months, has significantly decreased Covid-19 lethality. Furthermore, almost all severely ill patients show a marked rise in D-dimers which is unequivocal evidence that clotting has occurred somewhere in the body.

Several days into a severe Covid-19 infection, “exudate” macrophages that have assembled in response to a SARS-CoV-2 infection of alveolar lung epithelium attack and destroy the virally infected cells. In mouse models of lethal influenza virus pneumonia this “attack of the macrophages” occurs between the fifth and the seventh day of infection.[3] There is good evidence that, in Covid-19, a similar process takes place. That “good evidence” consists of a bloodstream blizzard of oligomeric fibrin that in severe Covid-19 pneumonia typically makes an appearance seven to ten days into the viremia. It is significant to note that in the animal viral pneumonitis model, where the macrophage attack occurs between day five and day seven, the attack takes place two to three days after the influenza virus titer has peaked; it is, therefore, not a direct response to viral overload. However, once the “bloodstream blizzard” of oligomeric

fibrin appears, the pathophysiology of Covid pneumonia is no longer primarily that of a viral disease; it is now largely that of a clotting disorder.

Fibrin results from the enzymatic action of thrombin on fibrinogen. Where can this thrombin be coming from? Given the destruction of respiratory epithelium that Covid-19 produces, the likeliest source is the dead and dying alveolar lining cells under attack by thromboplastin-rich alveolar macrophages.[4] Thromboplastin, also referred to as Tissue Factor (TF) initiates the extrinsic clotting pathway. Once initiated by TF, the extrinsic clotting pathway can produce thrombin in only a few seconds. If this is, indeed the source of the thrombin, it raises another question: why does this thrombin produce a "blood-stream blizzard" of oligomeric (short-chain and hence soluble) fibrin rather than the usual large, vessel-occluding clot?

This atypical clotting is, very likely the result of minute quantities of thrombin entering the bloodstream again and again—for repeatedly introducing minute quantities of thrombin into vigorously stirred, anticoagulated blood does produce fibrin oligomers of short enough chain length that they remain soluble. If the process is continued, a "blood-stream blizzard" of oligomeric fibrin in quantities similar to that seen in Covid-19 patients can be recreated on the laboratory bench. From this evidence it seems likely that, as each alveolus succumbs under Covid-19 attack, a minute amount of thrombin will result from activation of clotting initiated by thromboplastin-rich macrophages and other cellular debris. As this thrombin—and likely some thromboplastin as well—enters the pulmonary circulation, the small amount of the enzyme (thrombin) will result in only a few molecules of the product (fibrin) before it is diluted by ongoing blood flow.

This anomalous type of clotting has drawn scant attention thus far, for at least two reasons. 1. While it is underway there are often no immediate associated clinical symptoms. The lack of clinical symptoms occurs because most of the newly produced fibrin molecules remain, like the antecedent fibrinogen molecules, *in solution.* 2. When the earliest microclots do appear, the occlusion of arteriolar and/or capillary-sized vessels in widely scattered regions throughout the body will produce few localizing symptoms.

That microclots form, circulate and occlude vessels has been confirmed by supravital capillaroscopy in ventilator dependent Covid-19 patients.[5] As short-chain fibrin molecules lengthen by polymerization they become too long to remain in solution. It is microclots of this size—on the borderline between soluble and insoluble fibrin—that will first appear. Microclots of this size are too small to be detected by routinely available, non-invasive, diagnostic techniques.

Because the fibrin binding sites on short-chain fibrin oligomers are complexed to complementary sites on native fibrinogen molecules, they are not readily accessible to other short-chain fibrin molecules. This inaccessibility slows the growth of fibrin protofibrils and the formation of fibrin clots. These molecular aggregates between short-chain fibrin and native fibrinogen molecules are known as Soluble Fibrin Monomer Complexes[6] and, for convenience will be referred to as Soluble Fibrin (SF). Test methods for

detection of SF are not readily available, and the few methods that are available are not offered by most clinical laboratories.

Routine clotting assays such as those for quantifying fibrinogen levels will make no distinction between native fibrinogen and SF as the differences between intact fibrinogen molecules and SF molecules are minute. However, these tiny molecular changes result in a profound difference in molecular behavior. *Without further modification*, if the bloodstream concentration of SF is increased it will polymerize and precipitate out of solution, randomly forming clinically undetectable microclots throughout the body. The other molecular species (fibrinogen) is a normal protein constituent of blood and unless it is further modified it will circulate for days before being degraded and replaced.

In only a minority of COVID-19 patients do the high levels of SF lead to the formation of large, branching, three-dimensional, fibrin polymers—polymers so large that they show up in the vasculature as clinically recognized macroscopic clots. More often—even though some portion of the SF may have already achieved the size of fibrin protofibrils[7]—macroscopically visible clots do not form. The miniscule clots that do form are fragile, and, for the most part, rapidly dissolved by plasmin. The only evidence of their transient existence may be a rise in D-dimers over the next several hours. However, if a "bloodstream blizzard" of SF has supervened, the subsequent rise in D-dimers will not be subtle. Often it will be so extreme as to dramatically exceed the upper limits of the usually-reportable range for the D-dimer assay. In Covid-19 patients, D-dimers can remain at extremely high levels for 100 hours or more. Once this has occurred, death is extremely likely. However, it may be delayed for days or weeks while tissue downstream from occluded arterioles/capillaries in organ systems throughout the body undergoes coagulation necrosis. Death, when it does supervene, is often so far removed in time that it may appear unrelated to the episode of anomalous clotting that initiated the rapid rise in SF.

At least two clinical situations are known where soluble fibrin or some near equivalent is produced but where visible clots do not form. The first clinical situation arises because the goal is precisely *defibrination*. The intent is to deplete the body's entire supply of fibrinogen for therapeutic purposes—for anticoagulation. The agent employed is Ancrod[8], a procoagulant extract of the Malayan pit-viper venom. When this extract is administered (very slowly and in very carefully limited amounts) to adult humans, it—like thrombin—transforms fibrinogen into fibrin. However, the venom extract exposes active fibrin binding sites by cleaving only fibrinopeptide A from the fibrinogen molecules (as opposed to thrombin's cleavage of both fibrinopeptides A and B). Furthermore, Ancrod does not activate Factor XIII, so stabilization of fibrin clots does not take place. Consequently, the clots that do form are fragile and break up almost immediately. Although the goal of defibrination is readily achieved there is scant evidence that Ancrod-induced defibrination is therapeutically useful.[9,10]

A second clinical situation involving SF is the disseminated intravascular coagulation—DIC—that can develop (fortunately briefly) in patients during liver transplantation surgery. If SF is going to appear at all, it will usually make its appearance just after reperfusion of the transplanted liver, when residual dead and dying cells from the transplanted liver are washed into the transplant recipient's vasculature. (This is

occasionally and catastrophically accompanied by the sudden appearance of large clots in the heart and great vessels.) If the newly transplanted liver is healthy and begins functioning immediately, the SF levels will generally drop back towards the normal range over the next 60 minutes or so.

A similar mechanism appears to be responsible for the generation of SF in patients with severe Covid-19 pneumonia. SARS-CoV-2 is a respiratory virus; it attacks respiratory epithelium. It typically causes necrosis of the infected cells as the cellular machinery is diverted to viral replication and the host cell dies. Should hemorrhage into the damaged alveolus occur (at autopsy in severe Covid-19 pneumonia alveolar hemorrhage is widespread), dead and dying alveolar cells, along with TF-rich macrophages will activate the extrinsic clotting pathway on contact. However, instead of a massive infusion of dead and dying cells as occurs in liver transplantation, this thrombin generation and/or infusion of necrotic cells into the pulmonary circulation will occur, one dying alveolus at a time.

The Covid-19 virus, having coopted an anomalous variant of clotting to produce SF, can now extend its damaging effects to the entire body. Wherever the SF molecules encounter other fibrin oligomers—due to conditions such as cooling in the extremities, vascular narrowing, roughened endothelium or other factors that result in turbulence or non-laminar flow, or simply extremely high levels of SF—the short chains of oligomeric fibrin can encounter one another, polymerize, lengthen and form two-stranded protofibrils 0.5–0.6 μm in length. These protofibrils correspond to ~ 20–25 monomers[11] and are no longer soluble. Prior to this development the monomers and shorter polymers have been held in soluble form while complexed to carrier fibrinogen molecules. Now, however, as the protofibrils lengthen they become long enough to self-interact and aggregate laterally. A sol to gel transition occurs and microclots form.[12] Even after gelation, new fibers and branching points continue to develop.[13] As this process continues, the previously soluble SF now forms microclots, capable of occluding small blood vessels throughout the body. As already noted, most such occlusions are rapidly cleared by clot lysis or by remodeling of the fibrin microclot prior to stabilization by Factor XIII.[14] But if those microclots persist for more than several minutes, the tissue supplied by the occluded blood vessel, may die.

A clotting process, initiated in the lungs of Covid-19 patients, that distributes SF throughout the body is not merely a hypothetical construct. High levels of SF exist in the blood of severely ill Covid-pneumonia patients and can be readily demonstrated with an appropriate assay. Even though it is likely formed only in the lungs, it is present in, and can be precipitated from, blood samples withdrawn from the arm veins or central catheters of such patients. It therefore exists throughout the entire bloodstream.

We report measurements of these oligomeric fibrin molecules in patients with severe Covid-19 pneumonia and document that the process of SF formation can result in whole body defibrination even though macroclots are not clinically or radiologically identified.

Materials And Methods

A common daily protocol for laboratory data on Covid-19 patients with or without ventilator assistance in an ICU ward specifies the measurement of Fibrinogen, D-dimers, Sedimentation rate, Ferritin, and High-Sensitivity C Reactive Protein. In our Medical Center the protocol also includes the option of Soluble Fibrin measurement.

Precipitation technique and measurement of oligomeric fibrin—reported as Soluble Fibrin Units (SFU)

Quantification of SF was performed as previously described.[15] Briefly, citrated whole blood was drawn by trauma-free venipuncture or through a central line after appropriate clearing. Samples were at all times maintained at 37˚C. Testing was performed by adding 150 μL well-mixed whole blood to 450 μL pre-warmed protamine sulfate reagent (0.4 mg/mL), subjecting the mixture to controlled turbulence (a complex rocking/rolling motion) and determining the time in seconds to first appearance of insoluble SF as gel or as clumps. Raw times were then converted to arbitrary soluble fibrin units (SFU) and the amount present expressed in sec^{-1} by dividing the time-to-appearance into 700. In our normal population, the reference range is 0–9 SFU for males; 0–11 SFU for females. Soluble fibrin levels in normal and patient blood samples are stable for up to 4 hours provided the temperature of the sample, throughout the entire period between phlebotomy and testing, is maintained at 37˚C. SF is partially cold-precipitable and elevated levels can drop markedly if the blood sample is allowed to cool between specimen acquisition and analysis. Rewarming the specimen to 37˚C does not resolubilize the precipitated SF.

Protamine sulphate is a strongly positively charged protein. When added to whole blood containing SF, it weakens the bonds between the fibrin monomers/oligomers and the complexed fibrinogen molecules.[16] The mechanical action to which the blood sample is subjected in the SF analyzer (and the hydraulic stress that results) potentiates further polymerization of the newly freed up fibrin oligomers until the polymers grow too large to remain in solution. The higher the concentration of SF in the sample, the more rapidly the precipitate appears. The endpoint for this assay is defined as the first appearance of fibrin gel or clumps ≥ 0.5 mm in diameter.

Measurement of SF levels and the usefulness of such data

The clinical laboratory assay that measures oligomeric fibrin levels is a Laboratory Developed Test (LDT)[17] as defined by the FDA's draft guidance document. The liver transplantation surgeons in our medical center needed an assay that would warn them of impending DIC before they were confronted with gross clots in the heart and great vessels or, alternatively, massive bleeding. None of the available methods took into account the cold sensitivity of the parameter under measurement,[18] nor were any of the then extant laboratory assays rapid enough (≤ 15 minutes) to provide useful estimates of SF levels to the surgeons while they were in the midst of a liver transplant.[19] To address surgical needs and overcome deficiencies with available tests, we developed the Rapid SF assay. During surgery, it is performed at 60-minute intervals in the transplant surgery suite on whole blood samples maintained at body temperature throughout sample acquisition, transportation and testing. Testing can be performed immediately

following sample collection without any additional specimen processing. This was the assay that was made available to physicians attending severely ill Covid-19 patients.[15]

Results

SF Levels in Three Covid-19 pneumonia patients

Table 1 summarizes the anticoagulation regimen and pertinent laboratory test results on three Covid-19 patients in the intensive care unit. Permission for use of this anonymized data was obtained from the Loma Linda University Institutional Review Board. Two of these three patients are now deceased, both dying in multi-organ failure. As of the time of writing, one remains alive—more than 7 months post-infection—but has suffered a stroke, is wheelchair bound and breathes via a tracheostomy. The pattern of the laboratory values as each case progressed is interesting and possibly instructive. It is unquestionable that patients #1 and #2 both underwent defibrination over ~ 4 days. That defibrination occurred is evidenced by the decrease in fibrinogen levels, with fibrinolysis confirmed by the D-dimer results. Fibrinogen levels in patient #1 decreased from 686 to 76 mg/dL between days 10–14 of Covid-19 pneumonia. In patient #2, fibrinogen dropped from 686 to 178 mg/dL between days 8–13. D-dimers, on most days while defibrination was progressing, exceeded the upper limit of the laboratory's reportable range (> 21.0 µg/ml). This level is ~ 50x the upper end of the reference range for this assay (0.4 µg/ml).

All three patients showed extremely high ferritin levels (reference range 12–350 ng/mL). This finding is common in Covid-19 patients with moderate to severe pneumonia. Ferritin is an acute-phase protein and it likely also reflects the activity of activated macrophages.[20]

SF levels in patient #1 were below detection limits on the day of admission (day 10 of illness). SF levels this low are common in patients receiving "prophylactic" heparin (i.e. 40 mg Lovenox q.d.). This patient was prophylactically anticoagulated with Lovenox on the day of admission (Day 10 of illness). Given the undetectable SF levels that were the result of this minimal anticoagulation, no further assays were ordered until day 13. By then, defibrination had occurred and fibrinogen had dropped from 686 to 76 mg/dL.

Patient #3 was not given heparin on admission as this patient was fully anticoagulated with Coumadin (INR 3.5) for a coexisting cardiovascular condition. Considering the attendant procoagulant threat of Vitamin K administration and/or of Factors II, VII, IX and X transfusions (and that the patient was already fully anticoagulated), Coumadin was not reversed and no heparin was given. As can be seen from subsequent laboratory data, an INR of 3.5 did not inhibit the generation of SF in this patient. On day 3, in view of the persistently high levels of D-dimer and SF, Vitamin K was administered and the patient was placed on a heparin drip. Following these actions, the defibrination process slowed significantly.

Discussion

The fact that SF is mostly soluble does not mean it is innocuous. If fragile microclots are forming and dissolving throughout the circulation, then fragile microclots may *temporarily* occlude random portions of the microvasculature throughout the body. The behavior of these delicate early microclots is likely influenced by two different, but well studied, mechanisms. 1. Soluble fibrin monomer complexes, protofibrils and early fibrin clots are much more dynamic than was first realized. Prior to Factor XIII-induced crosslinking, monomers/oligomers can rapidly dissociate from or insert themselves into other developing fibrin structures. If blood flow is rapid enough, dissociated fibrin monomers/oligomers will be carried away, thereby potentially reducing the developing blockage.[14] 2. Plasmin-induced fibrinolysis can rapidly break down delicate microclots. When this occurs D-dimers and other fibrin degradation products will be produced. However, if the anomalous clotting process results only in microclots there will be scant or absent x-ray and autopsy evidence that clots were ever present.

Such transiently-present microclots would account for many, if not most, of the bizarre manifestations of Covid-19—both during the acute phase of the disease itself and, in some unfortunate patients (the post-Covid syndrome sufferers), for weeks or months afterwards. These manifestations would be the delayed effects of widespread—even if largely temporary—microvascular occlusions. Most of these micro-occlusions will likely dissipate after only a transitory existence; however, those that do not immediately dissipate will cause coagulation necrosis and death of the tissue downstream from the more-than-transitory occlusion.

It is clearly quite possible for a *respiratory* virus to damage heart, liver, kidneys, brain, bring on diarrhea and cause skin lesions that look like frostbite if that virus, by coopting the clotting system, is capable of generating large quantities of SF in the bloodstream. If those fibrin molecules are of short chain-length only, and if they are complexed to native fibrinogen so that they remain in solution, they have access to all parts of the body. Whether the virus itself travels along with the oligomeric fibrin/fibrinogen complexes remains to be determined. We think that it is unlikely that a virus, optimized for replication in respiratory epithelium, is capable of infecting and proliferating in the plethora of cell types that are affected in Covid-19 patients. Viral particles, though, may well be detected in the debris from virally damaged alveolar lining cells that have entered the circulation. Elevated SF levels, however, are certainly capable of damaging all cell types in the body via sporadic occlusion of portions of the microcirculation.

How this might play out seems worthy of further—admittedly speculative—consideration. Low levels of SF are a normal constituent of the blood stream in health. Where it is generated and what the variations within the normal range signify we do not yet know, and further research is called for. It is entirely possible that the levels (0-11 SFU) that span the normal range are a part of the physiological catabolism of normal fibrinogen. The Kupffer cells of the liver are thought to constitute the clearance mechanism for activated clotting factors; they likely serve a similar function for “activated” fibrinogen, i.e. SF.[21] Whatever the mechanism that is operative in the degradation and disposal of normal levels of SF, these physiological mechanisms are clearly overwhelmed when those levels rise several-fold.

We believe it to be the case that in Covid-19 patients SF forms primarily in the lungs and then travels throughout the body. It is not unreasonable to assume that transient, microscopic clotting events are occurring throughout the bodies of such patients, even if there is no physical or radiologic evidence of clots. Most often, the clots are tiny and although observable via capillaroscopy will not be otherwise detectable clinically. Their presence has now been confirmed in extrapulmonary tissue in living, ventilator-dependent, Covid-19 ICU patients.[5] Eleven of thirteen such patients (85%) demonstrated evidence of circulating microvascular thrombi, with 31% showing completely stagnated capillaries. On three of these patients, an abrupt thromboembolic obstruction was captured on video as it occurred.

SF is present in large amounts in severely ill Covid-19 patients and an assay system exists that is capable of quantifying it. Furthermore, SF is capable of precipitating and forming microclots throughout the body. That such microclots exist in Covid-19 patients has been confirmed by direct visualization. These transiently present, potentially widespread, “invisible clots” would provide a plausible explanation for the unquestionably beneficial effects of routine heparin administration in Covid-19 patients.

Finally, there is more than one potential reason for heparin’s effectiveness. Heparin is an anticoagulant and will neutralize thrombin. It also releases Tissue Factor Pathway Inhibitor (TFPI) which directly interferes with the ability of TF to initiate the extrinsic clotting pathway.[22] Cooption of an anomalous clotting pathway would go a long way to accounting for how a respiratory virus can be responsible for the protean manifestations that characterize the harrowing disease known as Covid-19.

Table

Please see the supplementary files section to view the table.

Declarations

Acknowledgements

We acknowledge Melanie Thornburg for design support for Fig. 1 and Sheryl Aka for meticulous experimental realization.

Competing Interests

Both authors are holders of a patent (now expired) for an original version of the assay device that, among other assays, measured soluble fibrin. Both authors have filed for patent protection on an updated version of a similar automated assay instrument.

Additional Information

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Figures

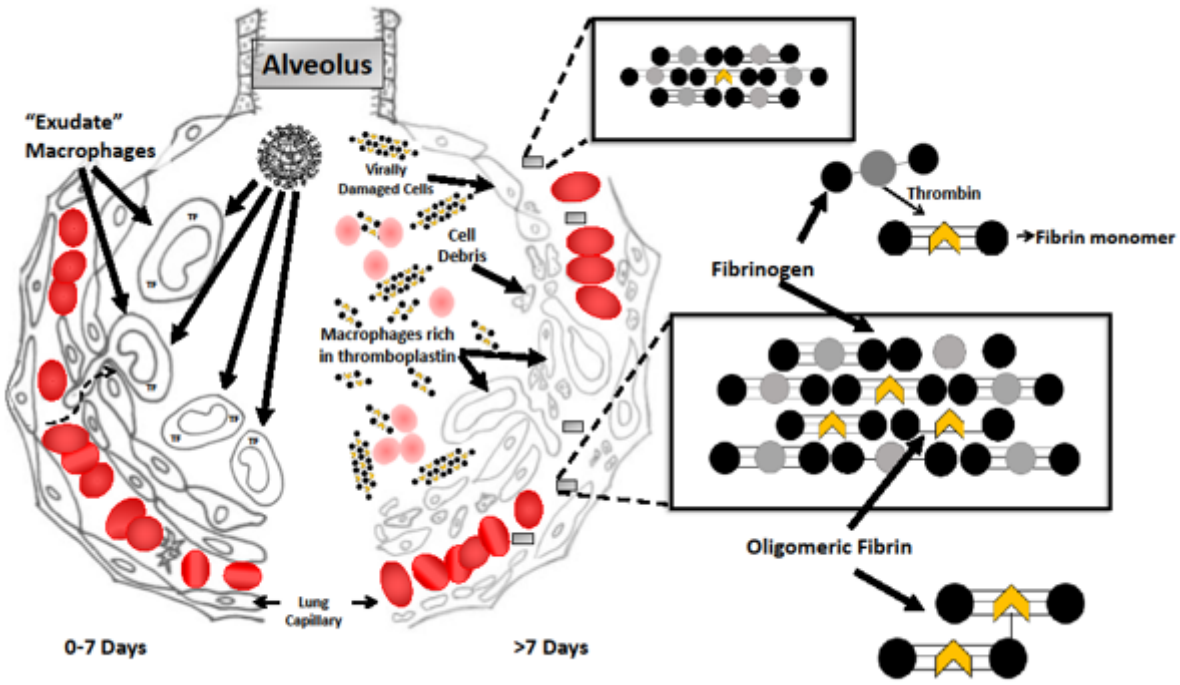

Figure 1

A drawing of the intra-alveolar sequence of events during Covid-19 pneumonia. The left half depicts events during the early phase of disease when the virus is multiplying in alveolar lining cells with a response to the infection from “exudate macrophages”. The right half depicts events after the gathered macrophages have attacked the alveolar lining cells, intra-alveolar hemorrhage has occurred with clotting

and thrombin is being infused back into the pulmonary circulation. The blow-up panels showing molecular structure depict the fibrin-fibrinogen complexes in the pulmonary capillaries that are now free to circulate systemically.

Supplementary Files

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