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Title:

Dramatic Cytokine Storm Reversal with an Over the Counter NMN Cocktail

Abstract:

Oral nicotinamide mononucleotide (NMN) with boosters may naturally trigger anti-inflammation immune systems able to arrest and reverse cytokine storm. A COVID-19 positive case is described with a strong temporal relationship between NMN cocktail use and clinical improvement - more remarkably this case exhibits an unusually rapid and thorough clinical turnaround. Oral NMN with boosters deserve further study in COVID-19 associated cytokine storm.

Dramatic Cytokine Storm Reversal with an Over the Counter NMN Cocktail

By Robert Huizenga MD

A 55-year-old white female presented on 3/16/2020 with one day history of body aches, choking cough and fever to 100.2ºF. The SARS-CoV-2 test was positive. She was treated with Tylenol as needed for fevers.

On day 3 she complained of new myalgias and chest aching.

On day 7 she was bedridden with chest pain, shortness of breath, cough and high fevers (Tmax 102º F). Her room air (RA) O2 % sat was 93-95. A CXR was normal (Figure 1).

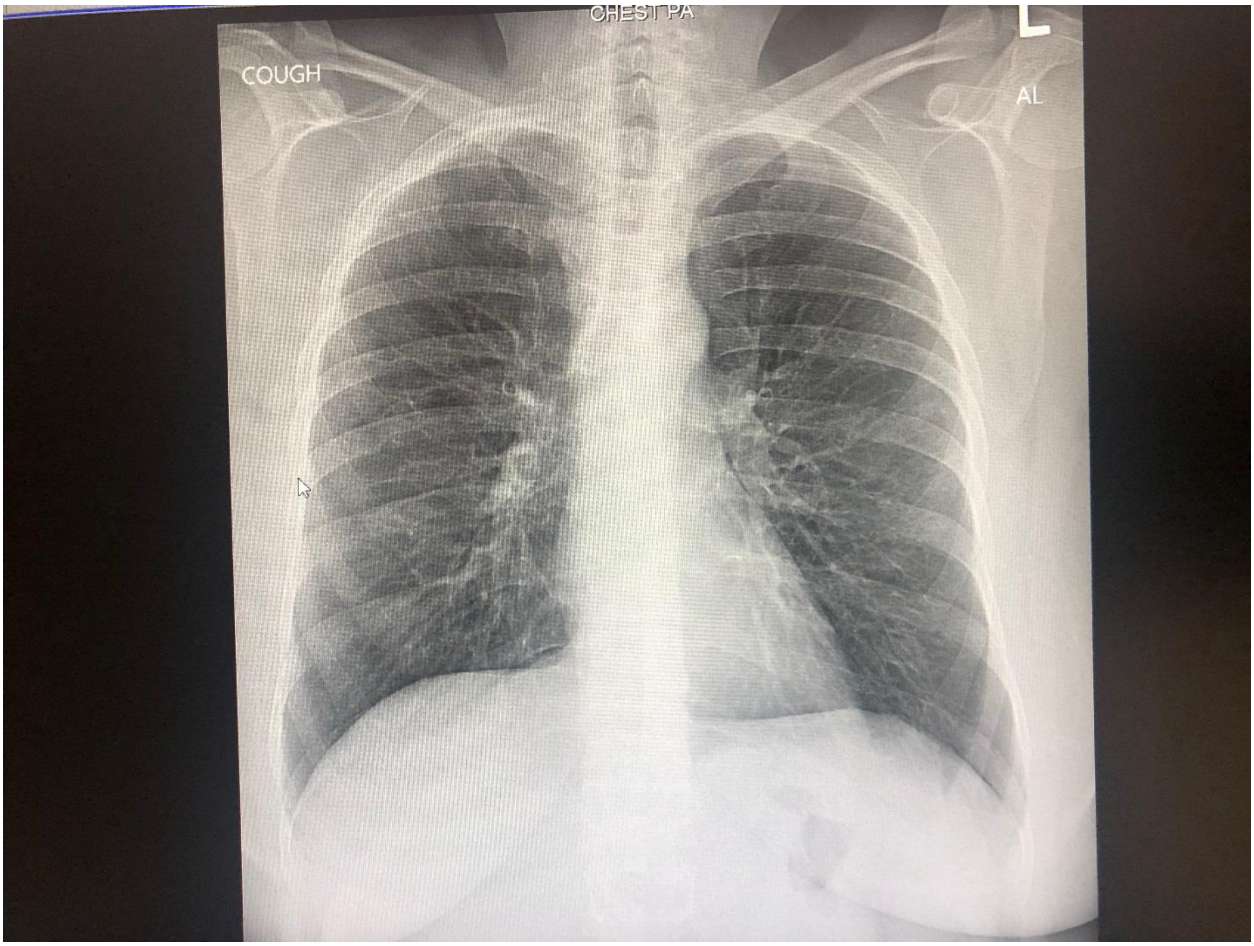

Figure 1: Day #7, chest x-ray normal

On day 8 her fever increased to 102.5º F. She was prescribed Zithromax, Hydroxychloroquine and Zinc.

On day 11 she further deteriorated three days into her triple therapy regimine. Her QTc interval was normal (420 ms). Her RA O2 % sat decreased to 90, her temp rose to 103º F with shortness of breath and debilitating body aches. CXR revealed new bilateral infiltrates (Figure 2).

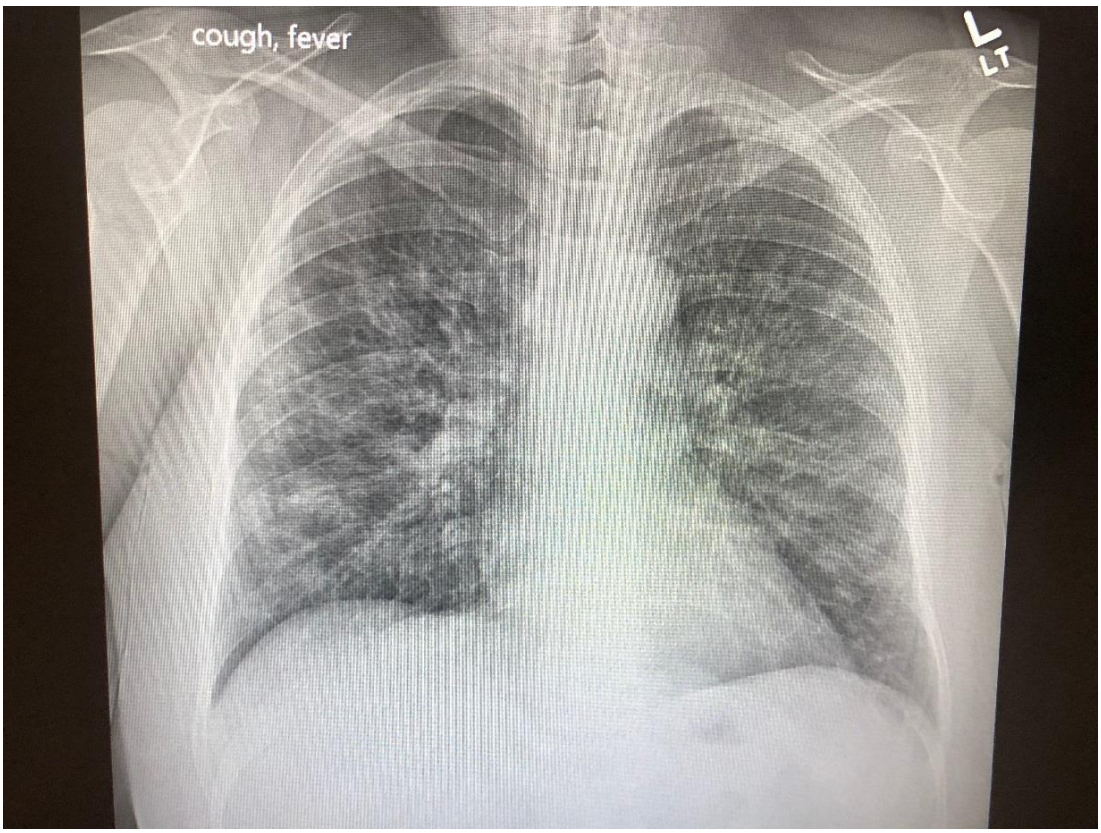

Figure 2: Day #11, chest x-ray with new onset bilateral pneumonia

She was admitted into Cedars Sinai Medical Center. Her BMI was 30 and her history was positive for a recent uneventful elective arm plastic surgery and a past history of episodic hives and allergic reactions to Ivermectin and Keflex. Admission labs were notable for astronomically elevated CRP (217 mg/L), Il-6 (56 pg/mL), TNF-alpha (7.4 ng/mL) and myoglobin (>500 ng/mL) with absolute lymphopenia (490cells/µL).

On day 12 and 13 the patient further clinically deteriorated; she subjectively felt she was unable to breathe. Her RA oxygenation worsened and increased bilateral pneumonia was noted on CXR (Figure 3).

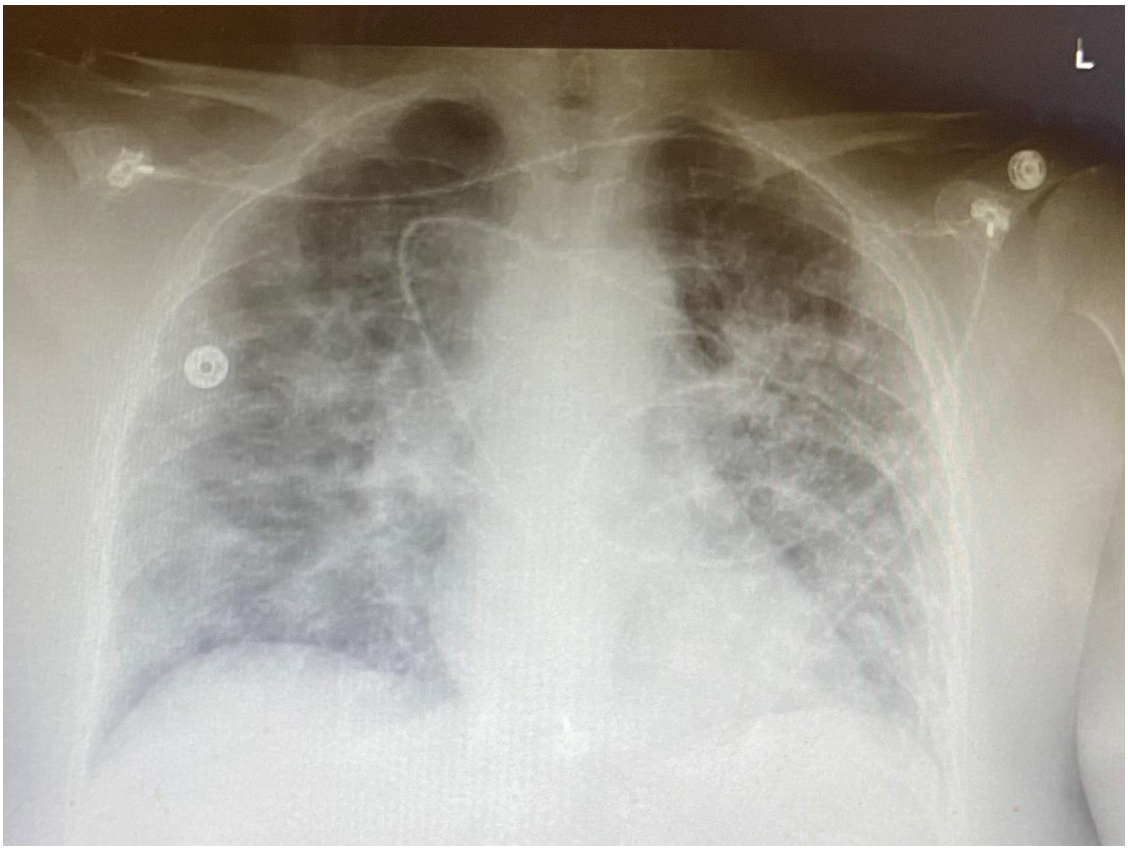

Figure 3: Day #13, chest x-ray 36 hours after hospital admission with worsening bilateral pulmonary infiltrates

A repeat nasopharyngeal SARS-CoV-2 test was done attempting to differentiate between high amounts of virus (inadequate anti-viral treatment) or low or absent viral loads (deterioration based on “cytokine storm”). Her test revealed negligible (<4 copies/µl) nasopharyngeal virus (Figure 4).

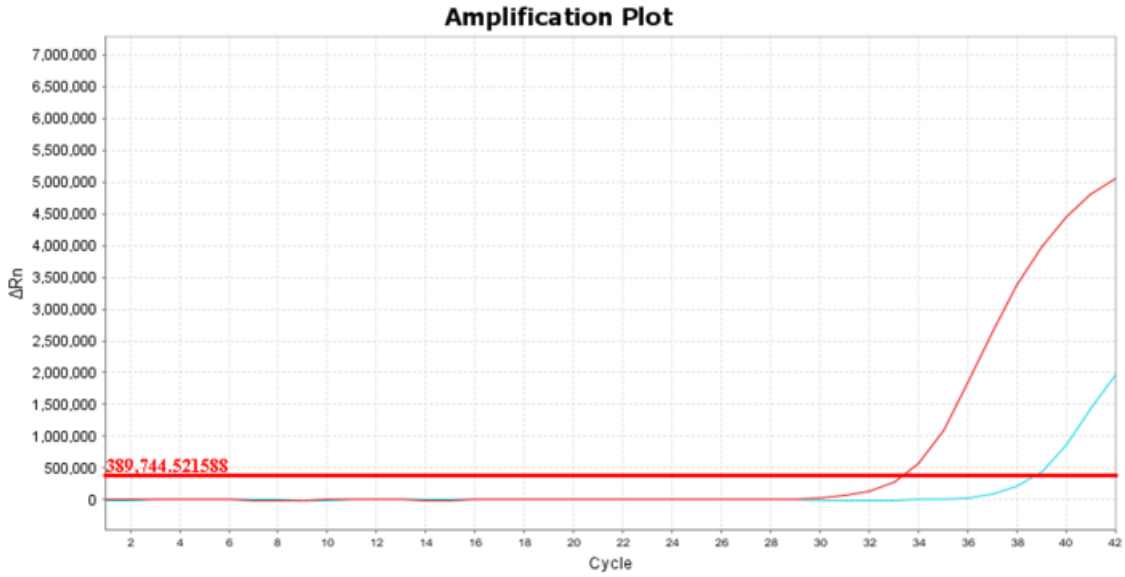

Fig 4: Amplification plot showing amplification curves of the positive control (red) and the patient's day 13 sample (aqua). The control (100 copies/uL) crossed the threshold at 33.2 cycles while the patient's sample crossed at 38.9 cycles. This equates to a value that is lower than the reported linearity of the assay (<4 copies/uL). (Curtesy Dr E Vail)

Her deterioration was therefore felt to be the result of cytokine storm. Tocilizumab – a humanized monoclonal antibody that inhibits ligand binding to the human interleukin-6 receptor (IL-6R) used for juvenile rheumatoid arthritis and used now experimentally for COVID-19 associated cytokine storm – was requested. However, strict hospital protocol prohibited the use of this drug outside of the ICU – and because her O2 % sat on high flow nasal O2 (6 liters) was still ≥ 90 (i.e. 91-92) - she did not meet criteria for ICU transfer.

She therefore agreed to begin over the counter (OTC) nicotinamide mononucleotide (NMN) with betaine and NaCl drunk in 400cc water known to lower IL-6. The BID dosage was timed in syn with the patient's presumed diurnal circadian rhythm peaks while continuing the daily zinc sulfate (Table 1).

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Covid19 Test		Pos											Pos (<4 copies/uL)							Neg			(+)IgG/IgM
Hospitalized											admit 5pm						home 10am						serology
Bedridden						yes	yes	yes	yes	yes	yes	yes	yes	walked	walked	walked	walked			no			near Nl
temp (Tmax)	100.2					101.5	102.0	102.5	102.6	102.8	103.0	103.0	103.1	102.3	99.0	98.9	98.3			98.8			98.6
cough	choking cough			new chest "ache"											reduction cough								
CXR							NL				Bilat Infilt		Worse Bilat Infilt				Better Bilat Infilt						Better Bilat Infilt
O2 % Sat on RA x 10 min							93				89-90	88	84	88	93	94	96			97			97
Abs Lymphs											490	291	540				1029			1218			
CRP											217	201	193	205	134	69	36			7.4			
IL6											56		52							3.2			
TNFalpha											7.4												
troponin/ QT(c) interval											NL												
azithromycin Qd								500	250	250	250	250											
hydroxychloroc mg TID								200	200	200	200	200	200										
Zinc sulfate Qd								220	220	220	220	220	220	220	220	220	220	220	220	220	220	220	220
NMN/Betaine/NaCl (gr BID												pm onl	1.67	1.67	1.67	1.67	1.67	1.25	1.25	1.25	1.25	1.25	1.25

Table 1

On day 14, after two weeks of continuous fever, the patient turned afebrile. On day 15-17, her clinical signs (shortness of breath, body aches, RA oxygenation, CXR) and prognostic laboratory markers (CRP and absolute lymphocyte count) rapidly and dramatically improved.

On day 17 she was discharged home on oral NMN/betaine/NaCl/Zinc BID with near normal oxygenation despite residual (improving) bilateral pneumonias (Figure 5).

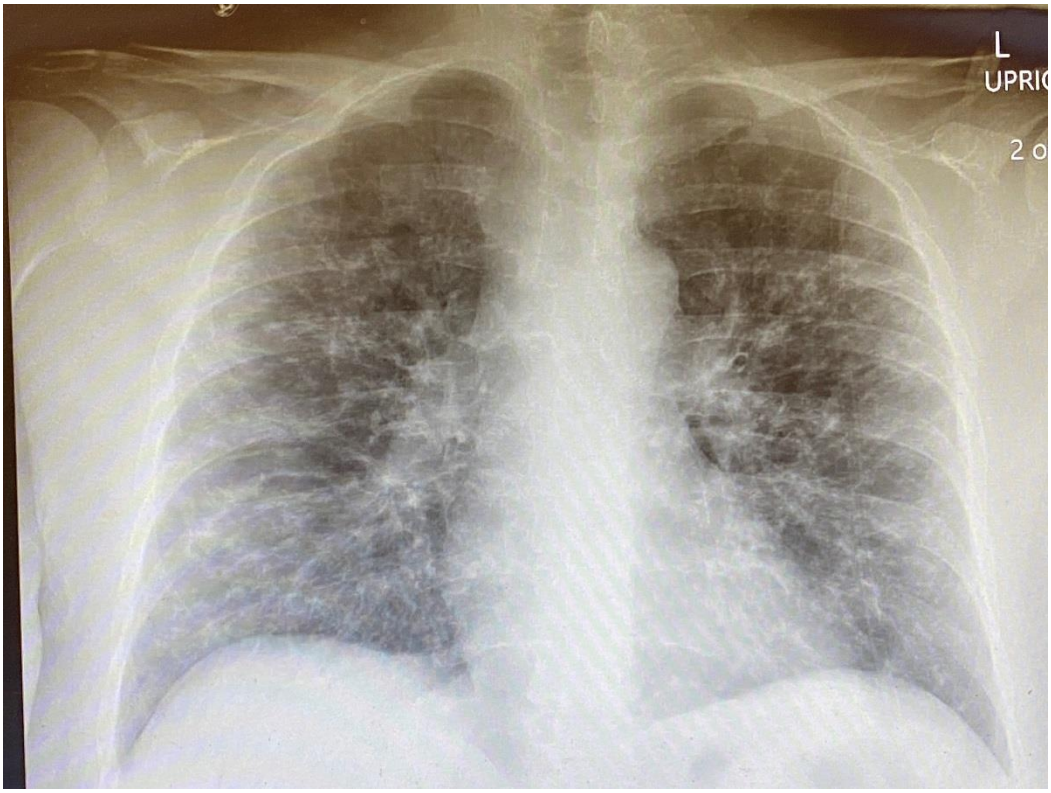

Figure 5: Day #17, chest x-ray with improving bilateral infiltrates.

On day 20, her third day home, she felt stronger and was walking multiple times a day. Her nasopharyngeal SARS-CoV-2 test was negative. Her CRP and IL-6 decreased to 7.4 and 3.2 respectively.

On day 23, she was asymptomatic; her COVID-19 IgG/IgM rapid serology was positive for both IgG and IgM. Her CXR revealed a small amount of residual bilateral pneumonia (Figure 6)

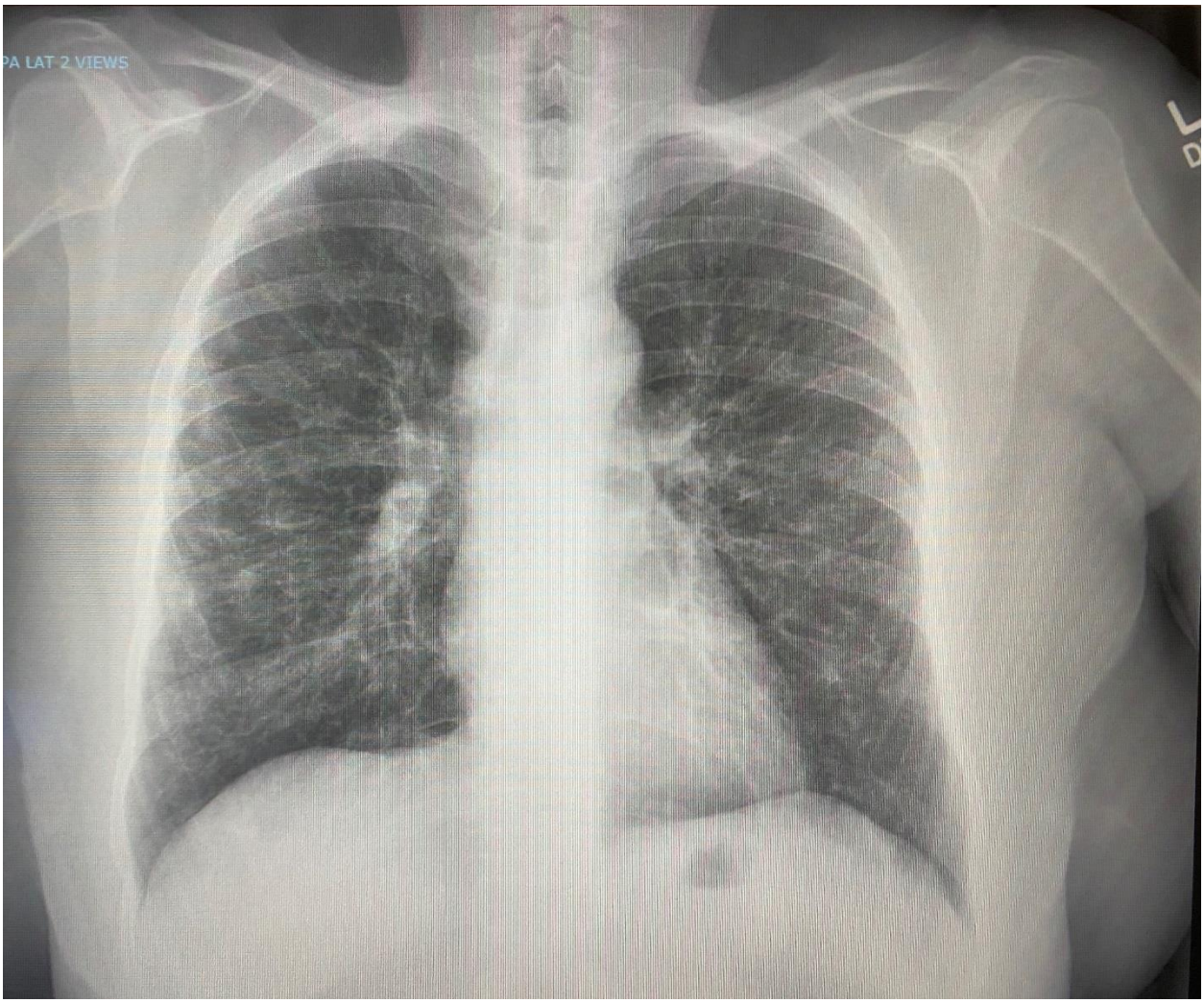

Figure 6: Day #23, chest x-ray improved with remaining predominantly peripheral bilateral infiltrates

Subsequent to this patient, this NMN cocktail has been given to two other elderly COVID positive outpatients after or concurrent with “triple therapy” with subjective symptomatic improvements of the following within 36 to 48 hours: fever, chest pressure, cough, headaches and low energy.

Discussion:

Disease fatality associated with COVID19 – like with SARS, Ebola and dengue fever - can often be attributed to cytokine storm: an exaggerated pro-inflammatory response with lymphocytopenia, elevated IL-6 and CRP levels giving rise to complex pulmonary, cardiac and hematologic conditions[1]. COVID-19 severity and lethality are substantially higher in the population aged 50 and older, especially those with co-morbid "aging" conditions like obesity, hypertension, diabetes, chronic lung conditions and neurologic disease.

There is currently no proven treatment for COVID-19. The experimental anti-SARS-CoV-2 "triple therapy" - hydroxychloroquine, Zithromax, zinc – was used in this case and of note, the nasal viral load was negligible at the end of the 6 day therapy despite clear clinical deterioration: sky-high cytokine output, persistent fevers and a swift pulmonary decline. By way of comparison, in a retrospective multicenter Chinese study of 150 confirmed SARS-CoV-2 cases [68 deaths (45%) and 82 discharged (55%)] the average (range) CRP and IL-6 levels of fatal cases respectively was 125(13-230) mg/L and 12(4-31) pgr/mL vs the discharged cases 35(1-125) mg/L and 7(2-13) pgr/mL (Figure 7, the IL-6 units should read pgr/mL)[2].

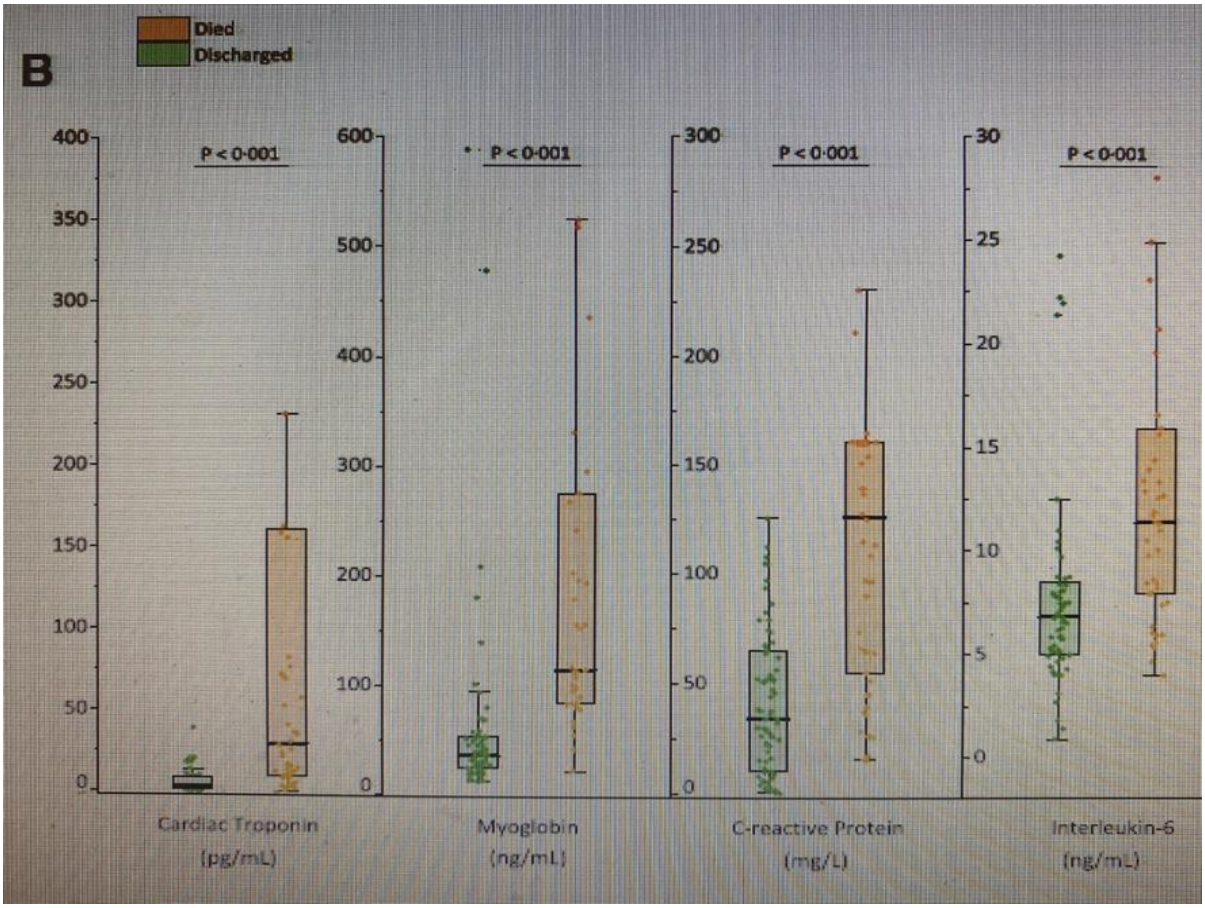

Figure 7 (table excerpted from Qiurong Ruan et al**. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China**. Intensive Care Med, 3/3/20)

This patient's admission inflammation levels [CRP (217 mg/L), IL-6 (56 pgr/mL) and myoglobin (>500)] strongly predicted a fatal outcome. Other recent American COVID-19 studies reported somewhat higher IL-6 values in hospitalized intensive care (ICU) cases – still, the risk of respiratory failure was 22-fold higher if the IL-6 level was ≥ 80 pgr/mL[3] and a CRP ≥ 200 was also a dire prognosticator[4].

Oral NMN/betaine/NaCl with zinc sulfate therapy was begun on the evening of day 12. Quite unexpectedly, 12 hours later, her absolute lymphocyte count increased by 85%. Thirty-six hours later, after two weeks of high fever, she abruptly became afebrile while simultaneous improvements in her O2 % sats and clinical condition were observed. Sixty hours after, her inflammation levels dramatically decreased.

NMN an OTC NAD-boosting compound with remarkable abilities to mitigate age-associated tissue and organ decline in mice, including an increase in immunity, blood flow, and protection of the kidney, liver and brain from disease and injury[5]. The compound, a precursor of NAD^+, in Phase I and II clinical trials, is safe and well tolerated in humans and has been documented to raise NAD^+ levels in whole blood (personal communication regarding human NMN trials, Dr. David Livingston, President of Metro International Biotech). NMN with nicotinamide feedback loop blockers (betaine) absorption boosters (NaCl) and Nrf2 boosters (including zinc sulfate) are also safe and well tolerated and have markedly lowered human cytokine levels (CRP, IL-6) in healthy elderly subjects (authors' preliminary 4-month clinical data).

COVID-19 complications may be reversible by NAD^+ repletion. Specifically, five often cited contributors to COVID-19 morbidity and mortality - the renin–angiotensin (RAS) signaling pathway, oxidative stress, reduced perfusion, endothelial dysfunction and cytokine storm - all involve NAD^+ depletion[6 7]. Furthermore, NAD^+ repletion enhances sirtuin activity, ancient defense enzymes that protect against a variety of viral pathogens [8]. Specifically, NAD+ repletion enhances PARP activity - enzymes directly involved in antiviral (and presumably anti- SARS-CoV-2) activities[9].Sirtuins also have pro-respiratory, bioenergetic, anti-inflammatory, immunosuppressive[10] and anti-vascular inflammation actions[11].

Tocilizumab (Actemra) – an IV infusion currently in limited supply costing nearly $3,000 per dose which this patient requested but was unable to get - looks promising in uncontrolled observational studies as treatment for COVID-19 associated cytokine storm. However, it may arrest the entire range of pro and anti-inflammatory IL-6 functions so drug timing to block only pro inflammatory IL-6 functions may be difficult. Also, reported side effects of IL-6R inhibitors include hindering the body's ability to fight off upper respiratory infections.

In contradistinction, elderly individuals on oral NMN /betaine/NaCl plus Nrf2 boosters were shown to transiently spike their inflammatory markers over two-fold when under viral attack (i.e. influenza) (authors preliminary 4-month clinical data) – possibly indicating a balance between viral attack mechanisms on one hand and tolerable collateral tissue damage on the other hand.

COVID-19 can have an undulating course, and the majority of hospitalized patients are able to be discharged. However, the recent article "Compassionate Use of Remdesivir for Patients with Severe Covid-19" first authored by a Cedars Sinai Medical Center colleague[12], is a stark reminder that persons with this patient's presentation (i.e. clinical deterioration requiring hospitalization with high flow nasal oxygenation approximately 12 days after symptom onset) are gravely ill. All five patients with similar presentations in the afore mentioned study (patients numbered 37 to 41 on that papers Figure 2) fared poorly despite an experimental 10-day course of the anti-viral Remdesivir – one died, one probably died and the three documented survivors all required prolonged 30 day hospitalizations!

In this patient's case, the temporal relationship between the administration of the NMN cocktail and the clinical turnaround – and more remarkably the rapidity and thoroughness of the improvement - suggests an OTC NMN cocktail may play a role in reversing potentially fatal cytokine storm.

Oral nicotinamide mononucleotide with boosters may naturally trigger anti-inflammation immune systems able to arrest and reverse cytokine storm. This case exhibits a compelling temporal relationship between NMN cocktail use and improvement from deteriorating COVID-19 bilateral pneumonias - more remarkably this case documents an unusually rapid and thorough clinical turnaround. Oral NMN with boosters deserve further study in COVID-19 associated cytokine storm.

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