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RESEARCH ARTICLE

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Rapid improvement in severe long COVID following perispinal etanercept

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ABSTRACT

Background: This study aimed to describe the neurological improvements in a patient with severe long COVID brain dysfunction following perispinal etanercept administration. Perispinal administration of etanercept, a novel method designed to enhance its brain delivery via carriage in the cerebrospinal venous system, has previously been shown to reduce chronic neurological dysfunction after stroke. Etanercept is a recombinant biologic that is capable of ameliorating two components of neuroinflammation: microglial activation and the excess bioactivity of tumor necrosis factor (TNF), a proinflammatory cytokine that is a key neuromodulator in the brain. Optimal synaptic and brain network function require physiological levels of TNF. Neuroinflammation, including brain microglial activation and excess central TNF, can be a consequence of stroke or peripheral infection, including infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19.

Methods: Standardized, validated measures, including the Montreal Cognitive Assessment, Beck Depression Index-II (BDI-II), Fatigue Assessment Scale, Controlled Oral Word Association Test, Trail Making Tests, Timed Finger-to-Nose Test, 20 m Self-Paced Walk Test, 5 Times Sit-to-Stand Test and Grip Strength measured with a Jamar Dynamometer were used to quantitate changes in cognition, depression, fatigue and neurological function after a single 25 mg perispinal etanercept dose in a patient with severe long COVID of 12 months duration.

Results: Following perispinal etanercept administration there was immediate neurological improvement. At 24 h, there were remarkable reductions in chronic post-COVID-19 fatigue and depression, and significant measurable improvements in cognition, executive function, phonemic verbal fluency, balance, gait, upper limb coordination and grip strength. Cognition, depression and fatigue were examined at 29 days; each remained substantially improved.

Conclusion: Perispinal etanercept is a promising treatment for the chronic neurologic dysfunction that may persist after resolution of acute COVID-19, including chronic cognitive dysfunction, fatigue, and depression. These results suggest that long COVID brain neuroinflammation is a potentially reversible pathology and viable treatment target. In view of the increasing unmet medical need, clinical trials of perispinal etanercept for long COVID are urgently necessary. The robust results of the present case suggest that perispinal etanercept clinical trials studying long COVID populations with severe fatigue, depression and cognitive dysfunction may have improved ability to detect a treatment effect. Positron emission tomographic methods that image brain microglial activation and measurements of cerebrospinal fluid proinflammatory cytokines may be useful for patient selection and correlation with treatment effects, as well as provide insight into the underlying pathophysiology.

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Long COVID; SARS-CoV-2; etanercept; perispinal; microglial activation; TNF; treatment

1. Introduction

Brain dysfunction caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may extend for months after infection has resolved[1,2]. Intractable cognitive dysfunction, depression, and fatigue are cardinal features of a post-viral syndrome named, variously, long COVID, post-COVID syndrome, post-acute sequelae of SARS-CoV-2 infection, or post-Covid-19 condition[1,2]. In contrast to acute infection, there is no specific pharmacological or non-pharmacological intervention that is currently recognized as being effective for long COVID[2].

Accumulating evidence suggests that long COVID brain dysfunction may be caused by over-activation of the brain's innate immune system, a pathological condition called neuroinflammation[3,4]. Two components of this deleterious immune response are activation of microglia, the predominant resident immune cells in the brain, and increased central levels of the key neuromodulator, tumor necrosis factor (TNF), a proinflammatory cytokine that regulates synaptic and network function in the brain[5–9]. Microglial activation and elevated levels of TNF can interact in a positive feed-forward autocrine loop that perpetuates neuroinflammation[10]. Following SARS-CoV-2 infection, neuroinflammation may occur and persist in the brain even in the absence of the virus[11].

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Table 1. Neurological and neuropsychological quantitative testing results before and after perispinal etanercept.

Clinical measures	Domain	Baseline Before PSE	30m After PSE	24h After PSE	29d After PSE	MCID[c]
Grip strength (R) (Kg)	Motor	14	32	32		5.0−6.5[41]
Grip strength (L) (Kg)	Motor	20	28	30		
BDI[a]	Depression	23/63		2/63	1/63	5[42]
FAS[a]	Fatigue	40/50		10/50	23/50	4[43]
TMT-B[a] (seconds)	Executive Fn.	52		29		
COWAT	Executive Fn.	52		64	70	2.8[44]
MOCA	Cognition	24/30		27/30	30/30	1.22−2.15[45]
MMSE	Cognition	26/30		29/30	30/30	3.72[46]
MACE	Cognition	21/30		30/30	29/30	
TMT-A[a]	Cognition	17 sec		14 sec		
20 m Self-Paced Walk Test[a]	Walking	22 sec		18 sec		
5 Times Sit-to- Stand Test[a]	Balance	13 sec		10 sec		2.3[47]
FTN-R (10 s)[b]	Upper Limb Coordination	6		15		
FTN-L (10 s)[b]		7		13.5		

[a]Note: Lower numerical score indicates clinical improvement for the measures marked with an asterisk.
[b]Values for the FTN test were the number of repetitions performed in 10 s.
[c]MCID values were derived from previous studies of different populations; MCID values for these measures have not been established for long COVID.
Abbreviations. R, right; L, left; Kg, kilograms; BDI, Beck Depression Inventory-II; FAS, Fatigue Assessment Scale; TMT-B, Trail Making Test; Part B; COWAT, Controlled Oral Word Association Test; MOCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; MACE, Military Acute Concussion Evaluation; TMT-A, Trail Making Test; Part A; FTN-R, Timed Finger-to-Nose Test, right upper extremity; FTN-L, Timed Finger-to-Nose Test, left upper extremity; Fn, Function; MCID, Minimal Clinically Important Difference; m, minutes; h, hours; d, days; PSE, perispinal etanercept;

Current evidence suggests that excess TNF is centrally involved in the pathogenesis of the brain dysfunction seen in a wide variety of clinical disorders[12,13]. Etanercept, a recombinant dimeric fusion protein, potently reduces the biological activity of excess TNF. Etanercept has also been found to reduce microglial activation in at least 15 experimental models[14–28]; in two of these models, involving influenza virus and Japanese encephalitis virus infection, etanercept also reduced mortality[21,22]. Perispinal administration of etanercept ("perispinal etanercept"), a novel method designed to enhance its delivery to the brain via carriage in the cerebrospinal venous system, is an emerging treatment for neuroinflammatory disorders associated with microglial activation and excess TNF[29–31]. Perispinal etanercept has previously been shown to reduce chronic neurological dysfunction after stroke, another disorder in which chronic neuroinflammation is thought to play a central role[32–37]. The therapeutic potential of etanercept and other biologic TNF inhibitors for SARS coronavirus infection has been previously recognized[13,38–40]. This study is the first to report the use of perispinal etanercept for treatment of long COVID neurological dysfunction. It details the clinical effects of perispinal etanercept in a patient with chronic, intractable and disabling cognitive dysfunction, fatigue and depression following COVID-19.

2. Methods

Standardized psychometric or neurological instruments that are widely used clinically to measure neurological and/or neuropsychological dysfunction were employed to evaluate the patient prior to and after treatment, as part of the clinic's usual medical practice (Table 1). These included measures of:

- *Cognition, including executive function*: Montreal Cognitive Assessment[48]; Mini-Mental State Examination (MMSE)[49]; Military Acute Concussion Evaluation (MACE)[50]; Trail Making Test, Parts A (TMT-A) and B (TMT-B)[51]; Controlled Oral Word Association Test (COWAT)[52];
- *Fatigue*: Fatigue Assessment Scale[43,53];
- *Depression*: Beck Depression Inventory-II (BDI-II)[42];
- *Motor strength, balance and gait*: Grip Strength measured with a Jamar hydraulic dynamometer[41]; Five Times Sit-to-Stand Test[47]; 20 Meter Self-Paced Walk Test[54];
- *Upper limb coordination*: Timed Finger to Nose Test[55].

2.1. Consent and ethics compliance

Ethics committee approval for this case study is not required under prevailing local medical and ethical standards. Written consent from the patient for publication of the case report, including the figure used, was obtained.

3. Case study

A 48-year-old woman presented to the clinic 12 months after developing COVID-19. Her chief complaints were severe difficulties with memory, concentration and fatigue, all of which had begun during the acute COVID-19 infection and had persisted without diminution for the entire 12-month period. Prior to COVID-19, she had been working full-time as a counselor and had not been vaccinated against COVID-19. The patient denied having a current or recent infection and denied fever, chills, shortness of breath, weight loss, easy bruising or bleeding. The patient's prolonged post-viral syndrome satisfied the World Health Organization criteria for "post-COVID condition (long COVID)[1]."

The patient's past medical history included mild asthma treated occasionally with an albuterol inhaler; seasonal allergic rhinitis; hypothyroidism treated with thyroid replacement; gastrointestinal reflux disease treated with pantoprazole; methylenetetrahydrofolate reductase deficiency treated with chronic methylfolate supplementation; post-hysterectomy bladder dysfunction treated with tamsulosin; hypertriglyceridemia; obesity; chronic neck, upper back and mid-back pain;

a history of a carcinoid tumor of the appendix that was surgically removed; and a history of repeated nephrolithiasis. There was no history of pre-existing cognitive dysfunction, fatigue, depression or other psychiatric disorder, drug or alcohol abuse, smoking, head trauma, immunosuppression, autoimmune disease, tuberculosis or a positive test for latent tuberculosis, or frequent infection.

The patient's COVID-19 had begun with a sore throat, nasal and sinus congestion, cough, shortness of breath and fatigue, without initial fever. Three days after symptoms began, at the primary care physician's office, the physician's notes indicated that the patient was afebrile, with pulse 102, respiratory rate 16, blood pressure 128/80, and oxygen saturation 96% on room air. The lungs were clear to auscultation, without rales or wheezes. There was no adenopathy. A rapid antigen test for SARS-CoV-2 (Abbott BinaxNow) was positive. The virus was not sequenced. However, infection occurred before the Delta or Omicron variants became prevalent in the U.S. The patient was discharged to home with a diagnosis of COVID-19, a prescription for an albuterol inhaler and a pulse oximeter, and pertinent instructions.

Over the course of the next week, fever to 39.7 °C, headache, nausea, vomiting, diarrhea, and diffuse myalgias developed. Ten days after symptom onset, dyspnea worsened and oxygen saturation dropped to 88% on room air measured with a pulse oximeter, and the patient went to the emergency department at a local hospital. A portable chest radiograph showed an "ill-defined airspace/ground-glass density of the right lung base." Computerized tomographic imaging of the chest, with and without contrast, showed "[e]xtensive airspace/ground-glass attenuation abnormality involving the dependent lungs and right upper lobe," without evidence of a proximal order pulmonary embolus (Figure 1). Dexamethasone 0.5 mg tablets once per day for 10 days were prescribed and the patient was discharged to home. Two days later the patient presented to another emergency department with chief complaints of right flank pain, hematuria and continuing dyspnea. On presentation to the emergency department, she was afebrile, heart rate 91/minute, respiratory rate 18/minute, and blood pressure 127/66. Blood oxygen saturation was measured with a pulse oximeter as 92% on room air. Computerized tomographic imaging of the chest, abdomen and pelvis showed "new diffuse bilateral ground-glass opacities involving the visualized portions of both lungs, no pleural effusion or pneumothorax," and a 4 mm non-obstructing lower pole stone in the left kidney.

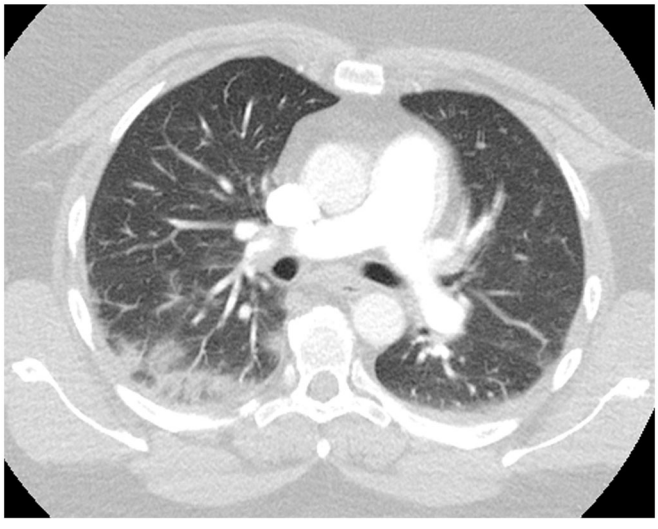

Figure 1. Chest computed tomography (CT), axial view, showing pulmonary infiltrates with ground-glass opacities in the right lung of the patient during acute COVID-19.

Two weeks after symptom onset, a rapid COVID-19 antigen test was negative, but the patient described continuing difficulty with short-term memory, mental concentration, mental organization, word finding and the inability to multitask. She reported hyposmia, hypogeusia, poor balance, decreased sensation in her right cheek, frequent headaches, slower speech, depression, and continuous debilitating mental and physical fatigue after COVID-19. All of these symptoms continued without abatement for months.

Ten months after her COVID-19 diagnosis, during a visit to her primary care physician, the patient's height was 1.62 meters, weight 99.79 kg, heart rate 104/minute, blood pressure 118/72, oxygen saturation 98% on room air; urinalysis, electrolytes, kidney and liver function tests, serum albumin, serum globulin, and complete blood count were all normal. All symptoms continued, including cognitive dysfunction interfering with both work and the normal activities of daily living, severe fatigue, and depression. Eleven months after COVID-19 diagnosis, additional laboratory testing was performed by her primary care physician to further evaluate unrelenting symptoms, including debilitating cognitive dysfunction, severe fatigue and depression: Chest radiographs, 2 views, and magnetic resonance imaging (MRI) of the brain, without contrast, were normal and a Mantoux tuberculin skin test was negative.

At 12 months the patient presented to the clinic. The patient's previous medical and imaging records were reviewed; the patient completed the Beck Depression Inventory-II and the Fatigue Assessment Scale. Vital signs were taken: blood pressure was 130/88, temperature 36.2 C, respiratory rate 16/minute, heart rate 90/minute. Lungs were clear to auscultation. Physical exam and neurological and neurocognitive testing were performed, with results detailed in Table 1. Written and oral informed consent for administration of perispinal etanercept was obtained. Perispinal etanercept 25 mg was administered external to the ligamentum flavum, by percutaneous extrathecal perispinal injection overlying the C7-T1 interspace of the spine utilizing sterile technique, followed by Trendelenburg positioning for 7 min, as previously described, as part of our usual practice of medicine[36].

4. Results

Following the single perispinal etanercept dose all clinical measures examined rapidly improved. Within 30 min of perispinal etanercept right hand grip strength more than doubled and left hand grip strength improved by 40% (Table 1). Within the first 30 min after treatment the patient

related subjective improvements in cognition, vision, hearing, taste, smell, speech, right hand motor control, shoulder spasticity, and right facial sensation.

After 24 h the patient returned to the clinic. The clinical measures quantitated just prior to treatment were retested. There were remarkable reductions in standardized measures of fatigue and depression and objective improvements in executive function, phonemic verbal fluency, cognition, balance, gait and upper limb coordination (Table 1). The patient reported subjective improvements in gait, walking and balance; that her thinking was clearer; vision less blurry; speech clearer; arm and leg strength improved; sensation in the right cheek improved; taste of coffee "stronger," and mood and "energy" improved.

Cognition, depression and fatigue were examined at 29 days; each domain, quantitated with the same standardized and validated measures, remained substantially improved (Table 1). There were no adverse effects from the treatment.

5. Discussion

In this patient with severe and disabling long COVID brain dysfunction, a single dose of perispinal etanercept resulted in immediate neurological improvement, with rapid, significant reduction in cognitive dysfunction, fatigue, and depression that was sustained over the 29 day period of observation. These results, and the accumulating evidence supporting the scientific rationale, highlight the need to conduct clinical trials with perispinal etanercept as a long COVID therapeutic.

Rapid improvement in chronic, intractable neurological dysfunction following perispinal etanercept has been reported over the course of two decades in a variety of neurological disorders, including traumatic brain injury, acquired brain injury, Alzheimer's disease, treatment-refractory cancer pain due to bone metastasis and intervertebral disc-related neuropathic pain, radiculopathy and sciatica[29,32,56–66]. In patients with chronic, neurological dysfunction after stroke, rapid improvements in cognition, fatigue, sensation, central post-stroke pain, taste, smell, vision, hearing, etc. have been documented[29,32,33,35,36]. The ability of perispinal etanercept to produce rapid neurological improvement in chronic stroke was confirmed in a double blind, placebo-controlled, randomized clinical trial performed at Griffith University in Australia[35]. The similarities of the rapid neurological effects of perispinal etanercept in long COVID and chronic stroke are striking.

A recent positron emission tomography study of chronic stroke patients and controls using a radiopharmaceutical targeting the translocator protein-18kDa (TSPO PET), a molecular marker of activated microglia, found extensive microglial activation in non-infarcted brain tissue in the chronic stroke patients[37]. This was the most recent of several studies that documented chronic microglial activation, and others that found evidence of global inflammation, in chronic stroke[34,67,68]. These findings, together with the evidence of brain microglial activation following SARS-CoV-2 infection, suggest that chronic neuroinflammation may be a shared pathology between chronic stroke and long COVID, and a viable therapeutic target for perispinal etanercept in both disorders.

This inference is also supported by an examination of the physiologic roles of TNF in the brain. TNF is one of the small group of molecules, called gliotransmitters, that are released by glia and modulate synaptic function[5,69–72]. In addition to TNF, known gliotransmitters include adenosine, ATP, D-serine, GABA, and glutamate[70,72]. Optimal synaptic and brain neuronal network function require the presence of physiological levels of TNF[69–72]. The mechanisms involved in TNF modulation of neuronal, synaptic, and network function include concentration-dependent effects of TNF on astrocyte glutamate release, TNF-mediated enhancement of synaptic efficacy (synaptic strength) by increasing surface expression of AMPA receptors, TNF mediation of synaptic scaling, and TNF mediation of homeostatic synaptic plasticity[69–72]. The ability of excess TNF to perturb brain function is highlighted by the results of early human clinical trials of recombinant human TNF, that documented severe, but reversible, CNS adverse effects, including confusion, headache, memory loss, expressive aphasia, seizures and fatigue severe enough to preclude hospital discharge, following intravenous infusion of the cytokine[73,74]. One may speculate that the immediate neurological improvement documented in the present case study is due to the rapid reduction in excess TNF bioactivity produced by binding of TNF by etanercept; and that prolonged clinical improvement (here seen at 29 days after treatment) is a consequence of etanercept's interruption of the known autocrine positive feedforward interaction that exists between TNF and microglia[10,75,76].

Excess levels of TNF in the cerebrospinal fluid (CSF) have been documented in stroke, traumatic brain injury and after SARS-CoV-2 infection[8,77,78]. TNF, the "master regulator" of the inflammatory response, also induces the production of other proinflammatory cytokines, such as interleukin-1 and interleukin-6. Measurements of cerebrospinal fluid TNF, interleukin-6, and interleukin-1, as well as TSPO PET imaging, might prove to be useful for patient selection and correlation with treatment effects, as well as provide insight into the pathophysiology underlying long COVID.

The psychometric or neurological instruments used to assess change in status following treatment in this patient are widely used clinically to measure neurological and/or neuropsychological dysfunction. Some of these measures have been used in previous studies examining the sequelae of SARS-CoV-2 infection: MOCA[49,79–82]; MMSE[49,79,81,83]; BDI-II[82,84]; COWAT[82]; TMT-A[82,83] and TMT-B[82–84]. The TMT-B measure that showed improvement after perispinal etanercept in the present case study was also selected as a key measure of cognition in a recent COVID-19 study performed using data from the UK Biobank[84].

The present findings accord with the results of a prospective, longitudinal cohort study of blood samples drawn from participants 5 months after hospital discharge following COVID-19, in which the investigators found persistent systemic inflammation, with higher levels of inflammatory

mediators in the "very severe" and the "moderate with cognitive impairment" clusters compared with the "mild cluster" [2]. The present findings also accord with previous data showing that peripheral infection or inflammation may lead to both microglial activation and increased production of TNF in the brain, and that central elevation of TNF may last far beyond the time when the peripheral inflammation resolves[75,76].

The chronic neurologic symptoms that had persisted in this patient prior to perispinal etanercept treatment are commonplace in long COVID. A recent longitudinal study of a cohort of participants without pre-existing neurologic conditions after COVID-19 found fatigue in 90%, memory impairment in 67%, decreased concentration in 60%, gait abnormalities in 27%, incoordination in 13%, and motor impairment in 10%[82]. Two-thirds of study participants had persistent neurologic symptoms at the 6-month follow-up, with over half reporting continued impact on quality of life[82].

There are limitations to the degree one can extrapolate from the enumerated clinical findings. This case study describes a single case and it is unknown to what extent this individual is representative of the entire population with severe long COVID. It is also not possible to determine to what extent practice effects, placebo effects or other confounding factors contributed to the observed results. The partial recurrence of fatigue at one month suggests that an additional perispinal etanercept dose or doses may be beneficial for some patients. Clinical trials will be necessary to further define the response to treatment in a larger population and establish optimal dose levels, dosing intervals, and duration of response to treatment. Nevertheless, the unusual rapidity, sustained nature, magnitude of improvement, and concurrence of improvements quantitated using well-known, standardized instruments across multiple neurological/neuropsychological domains (cognition, fatigue, depression, motor function, co-ordination) support the conclusion that the changes observed reflect a true therapeutic effect.

Initial Food and Drug Administration (FDA) approval of etanercept in 1998 was for chronic treatment of adults with rheumatoid arthritis. Since then, largely due to its efficacy and generally favorable safety profile, it has become widely used worldwide chronically by weekly or biweekly injection for additional rheumatologic disorders, in adults and children. Etanercept is contraindicated in sepsis, and according to the manufacturer's current package insert, when used for its labeled indications carries an increased risk of serious infections, including reactivation of latent tuberculosis, a small (less than 2%) risk of serious allergic reactions or anaphylaxis, a risk of injection site localized skin or soft tissue reactions, and, rarely, other serious adverse effects. The magnitude of these potential risks following a single dose of perispinal etanercept in an individual with long COVID who does not have underlying immunosuppression is uncertain. It would seem prudent to avoid etanercept use in individuals with a current infection, demyelinating disease, immunosuppression, lymphoma or leukemia. Further study in clinical trials will be necessary to gather additional safety data.

6. Conclusions

Perispinal etanercept is a promising treatment for the chronic neurologic dysfunction that may persist after resolution of acute COVID-19, including chronic cognitive dysfunction, fatigue, and depression. The present results suggest that long COVID neuroinflammation is a potentially reversible pathology and viable treatment target. They also suggest that investigation of other drugs or biologics that are capable of targeting aspects of brain neuroinflammation, including microglial activation and excess TNF, could be a productive direction for future long COVID research.

In view of the increasing unmet medical need, clinical trials of perispinal etanercept for long COVID are urgently necessary. The robust results of the present case suggest that perispinal etanercept clinical trials studying long COVID populations with severe fatigue, depression and cognitive dysfunction may have an improved ability to detect a treatment effect, in comparison with those trials studying a more diverse population. Prospective selection of those individuals most likely to respond to treatment for inclusion in the clinical trial is an enrichment strategy. Enrichment strategies are explicitly recommended by the FDA Center for Biologics Evaluation and Research to support determination of the efficacy of biologics in clinical trials[85]. Trial enrichment is of particular importance when studying heterogeneous populations, to improve the validity of the trial's conclusions[85].

Positron emission tomographic methods capable of imaging microglial activation and measurements of cerebrospinal fluid proinflammatory cytokines, including TNF, interleukin-6, and interleukin-1, may be useful for patient selection and correlation with treatment effects, as well as provide insight into the underlying pathophysiology.

Transparency

Declaration of funding

None.

Declaration of financial/other relationships

E.T. has multiple issued and pending U.S. and international patents covering delivery devices and methods of use of etanercept, including methods of perispinal administration, for treatment of neurological disorders, including neurological sequelae of stroke, brain injury, and SARS-CoV-2 infection, receives royalties from these patents, and utilizes these methods in his medical practice. R.S. and T.A.I. have no potential conflicts of interest. M.W. and S.L. are employed by the corresponding author's medical clinic but otherwise have no potential conflicts of interest. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors made a significant contribution to the work reported. E.T. conceived, designed, and drafted the majority of the manuscript. E.T., M.W., and S.L. acquired the data. R.S., T.A.I., M.W. and S.L. contributed to the drafting of the manuscript and the revisions. All authors critically reviewed the article, reviewed and agreed on all versions of the article

before submission and after revision, and take responsibility for its content.

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Informed consent

The patient gave written permission for publication of the manuscript and the included figure (Figure 1).

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