

Case 2/19: “A face-destroying disease”



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ABSTRACT

Case reported at the Clinical Cases Discussion Meeting of the University Hospital “Polydoro Ernani of São Thiago”, initiated by Profs. Jorge Dias de Matos, Marisa Helena César Coral and Rosemeri Maurici da Silva, July 2017. On June 13, 2019, in the medical school block, the case was presented and discussed: A 38-year-old male patient is followed at the rheumatology outpatient clinic with a destructive upper airway disease, pansinusopathy, positive ANCA and anti-proteinase 3. He is a chronic user of inhaled cocaine and corticosteroids. One day, he comes to the emergency room with acute headache and meningism. What is the diagnosis?

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Céline Schweri (resident in rheumatology): Good evening. A male patient, 38 years old, a bricklayer, married, first consulted at rheumatology outpatient clinic in September 2015, referred from the otorhinolaryngology outpatient clinic. He reported episodes of epistaxis for 2 years, with recurrent nasal obstruction and elimination of nasal crusts, progressive dysphagia and dysphonia, and generalized malaise and diffuse pain. He reported continued inhaled cocaine use for up to 20 years (having ceased for about 2 years, coinciding with the onset of symptoms - but admitting relapses of its use). He was also a smoker and a daily marijuana user. Past morbid history revealed peptic ulcer disease and one episode of upper gastrointestinal bleeding.

On physical examination, he was lucid, oriented, afebrile, anicteric, acyanotic, pale +++ / 4+. Vital signs were within normal range, cardiac and pulmonary auscultation revealed no abnormalities, as well as abdominal palpation. Face ectoscopy revealed the collapse of the nasal bridge (saddle nose), and rhinoscopy revealed destruction of the nasal septum.

He had laboratory tests made in May 2015. The blood count: hemoglobin of 5.6 g / dl, hypochromic and microcritic red blood cells, with RDW of 15%; leukogram with mild eosinophilia (510 eosinophils

/ mm³) and slightly elevated platelet counts (503,000 platelets / mm³). Normal creatinine, transaminases, canalicular enzymes and blood glucose. Negative treponemal and non-treponemal serologic tests for syphilis. Negative antinuclear antibodies. ANCA (antineutrophil cytoplasmic antibody) was positive with titer 1:40 and cytoplasmic pattern. Urine examination showed 4,000 granular cylinders per mm³. A chest x-ray was normal.

There was also the anatomopathological result of nasal biopsy performed in January 2015 by the colleague otorhinolaryngologist: “fibrosis surmounted by dense mononuclear and neutrophil infiltrate. PAS negative for fungi. Negative BAAR. There is no granuloma. Suppurative inflammatory process.”

An upper digestive endoscopy showed esophageal moniliasis, gastritis and duodenal ulcer. A magnetic resonance imaging of the sinuses showed extensive destruction of the nasal septum, middle and inferior nasal turbinates and inferior ethmoidal trabecularis. There was also pansinusopathy (frontal, maxillary and ethmoidal).

At this consultation, intravenous iron infusions, omeprazole, fluconazole, albendazole, sulfamethoxazole-trimethoprim and prednisone at a dose of 60 mg / day were prescribed. He was also advised to maintain cocaine withdrawal.



Figure 1. Ectoscopy of the face with nasal bridge collapse (saddle nose)

At the return visit, the patient was feeling better. There were anemia improvement (hemoglobin 10.2 g / dl) and normalization of eosinophil and platelet count. The urine test no longer showed cylindruria. HBsAg, anti-HCV and anti-HIV negative; anti-HBs was negative but anti-HBc IgG positive. ESR was 38 mm/h and C-reactive protein concentration was 12.4 mg/l. ANCA remained positive, titer 1:80, but this time described as perinuclear pattern.

Fabricio Neves (rheumatologist): We then had an adult male patient with a destructive process of the nasal septum, who was a user of inhaled cocaine, but with a disease that is not limited to the nasal septum. It includes the presence of diffuse inflammatory findings in the face with pansinusopathy, it has positive ANCA repeatedly and, at least in the first presentation, it had granular cylinders on urine examination.

The diagnostic dilemma we had initially was to understand if the patient had granulomatosis with polyangiitis (GPA) or if he had a facial destructive disease secondary to cocaine use without a concomitant chronic autoimmune disease. With this initial diagnostic doubt, the treatment approach was also intermediate, not to the extreme of initiating the potent immunosuppression of GPA treatment, but also not to the other extreme of merely indicating abstinence from cocaine use. Improvement in anemia and treatment of infectious complications certainly contributed, but I had the feeling that corticosteroids made him feel better, with reduced crusting and nasal discharge, facial pain, and systemic malaise, because by reducing the dose of prednisone I had to increase it sometimes due to a few exacerbations of these symptoms, always with improvement. However, exacerbations were always associated with relapse in cocaine use, as reported by the patient. So, after a few months of follow-up I got the impression: "I don't think it's GPA, I think exacerbations are always caused by cocaine use and get better very quickly with corticosteroid therapy".

Céline Schweri (resident in rheumatology): But does anyone think of any other diagnostic hypotheses? In the differential diagnosis of granulomatosis with polyangiitis, there are several granulomatous and non-granulomatous diseases that can affect the nose and paranasal sinuses. Among them, we have infectious causes (mycobacteriosis, including tuberculosis; leprosy; syphilis; fungal infections, such as paracoccidioidomycosis and histoplasmosis; protozoa, such as leishmaniasis; bacterial, such as

rhinoscleroma due to *Klebsiella*); neoplastic causes (nasal lymphoma most often, formerly called lethal midline granuloma; and also nasal carcinoma); and other autoimmune diseases (eosinophilic granulomatosis with polyangiitis, sarcoidosis and granulomatous rosacea). And finally, cocaine-induced injury.

Audience: The biopsy performed in this case said there was no granuloma.

Fabricio Neves (rheumatologist): Yes, there was no granuloma found in the biopsy. Some of the diseases listed in Dr. Céline's differential diagnosis are not even granulomatous, including cocaine-induced injury. However, it is noteworthy that repeat biopsy is very useful for differential diagnosis. This first biopsy showed no granuloma or neoplasia and was negative for mycobacteria and fungi. However, this does not rule out these etiologies completely, as in a grossly inflamed area eventually a first biopsy does not define the diagnosis. Especially when clinical evolution is not compatible with the suspected diagnosis, a second or third biopsy is required. This patient was not submitted to another biopsy, because initially he evolved well, with improvement of symptoms.

Céline Schweri (resident in rheumatology): Along the follow-up in rheumatology clinic, the corticosteroids were gradually tapered. The patient was also accompanied by the gastroenterology service for the management of peptic disease. In December 2016, after one year of follow-up, ANCA was repeated, which this time was non-reactive.

Fabricio Neves (rheumatologist): From then on, follow-up became erratic. I believe the patient learned that he could manage the symptoms of exacerbations by increasing the prednisone dose. Thus he began to treat himself and tolerated occasional cocaine use again. He returned to medical attention only when a more serious complication occurred.

Céline Schweri (resident in rheumatology): In October 2017, he sought emergency unit with asthenia, anorexia, fever, drowsiness, cough and worsening of purulent nasal discharge, with foul odor. He had severe headache and reported blackened stools suggestive of melena. He also complained of neck pain that radiated to the upper limbs with limitation of their movement. He was hospitalized, receiving antibiotic therapy for sinusitis and during hospitalization evolved with tetraparesis, worse on the right. In view of this, a cranial computed tomography was performed (which did not reveal brain abnormalities - there was pansinusopathy and destruction of the nasal septum, ethmoidal floor and nose bones) and computed tomography of the cervical spine. This revealed bone erosions in the C1 anterior arch and odontoid process, associated with a small collection with air foci, which promotes indentation in the bulbomedullary transition. He was evaluated by the neurosurgery service, which concluded that there was no immediate surgical emergency and indicated to associate dexamethasone for the treatment with long-term antibiotics. Gradually, the patient evolved with neurological improvement and full recovery of strength in all four limbs and was discharged weeks later.

He returned to the rheumatology outpatient clinic in May 2018, when ANCA was positive again, with a titer of 1:80 and a cytoplasmic pattern. At the time, anti-proteinase 3 antibody screening was positive (anti-myeloperoxidase was negative).

Audience: Does the positivity of these antibodies reinforce the diagnostic possibility of autoimmune disease?

Fabricio Neves (rheumatologist): At this moment I really considered again the possibility of GPA, but I still was not convinced of this. These antibodies have more specificity for systemic vasculitis than ANCA alone, but they do not have 100% specificity and may appear under other conditions. That was a learning for me with this case.

Céline Schveri (resident in rheumatology): A review of the literature showed that cocaine lesions can often course with mixed ANCA patterns, atypical ANCA, as well as anti-myeloperoxidase and anti-proteinase 3 positive.

Mayara Moraes (resident in neurology): So, he was hospitalized in 2017 with spinal cord compression due to an infectious and / or inflammatory process in C1 and again the follow-up of this patient was lost. He had only one or two outpatient consultations in this period from 2017 to 2019 and was still using cocaine. Now in April 2019 he returned with a new complaint.

He was admitted to the hospital emergency service. He had noticed that the neck pain was getting worse, with a decrease in right hemibody strength, in addition to having nausea and hyporexia. On the day he sought emergency he also had a left lower limb hypoesthesia. He had cough with purulent discharge, although he denied fever. He reported the alleged diagnosis of vasculitis that was being followed, and reported the use of drugs, including cocaine. He was taking prednisone 40mg a day, omeprazole and tramadol.

Physical examination showed normal vital signs. In cardiopulmonary auscultation there were no alterations, nor in the abdominal examination. On neurological examination he was alert, collaborative, with hemiparesis in right hemibody and decreased tactile sensitivity (hypoesthesia) in right hemibody and left lower limb, without cerebellar changes and without meningeal irritation.

At the emergency service laboratory test and chest X-ray were performed. He had no anemia, had mild leukocytosis with no left shift and platelets within the reference value. C-reactive protein was increased by 50 mg/l, with normal renal function and transaminases. HBV, HCV, HIV, and VDRL serology were still negative, and ANCA, which was also requested at emergency entrance, had a titer of 1:80 and a cytoplasmic pattern. The chest X-ray showed no nodules or consolidations.

Considering its previous history, it was initially thought of a possible new spinal cord compression, or a contiguous direct infection of the central nervous system, originated from the lesions of the oral cavity and upper airways. The initial plan on the day of arrival was to initiate piperacillin / tazobactam and methylprednisolone 40 mg / day, symptomatic medications to control nausea and pain, and to request magnetic resonance imaging of the skull and cervical region for reevaluation of the old lesion and verification of changes.

In the early days there was an improvement in cough and sputum, food acceptance and vital signs remained stable as on arrival, but the neurologic deficit remained.

Magnetic resonance imaging revealed a lesion with annular impregnation, with 17x11x15mm, diffusion-restricted content, intra-axial in the central portion of the bulb, compatible with brainstem abscess. There was an important edema of the surrounding cerebral parenchyma, which extended caudally through the medulla until it reached C4. In addition, an important edema and impregnation compromising the atlantoaxial joint, including signs of fusion, were

observed, suggesting an inflammatory / infectious process in this topography. He had destruction of the oral cavity and retropharyngeal region as well.

Again, the case was discussed with a neurosurgery team, with a decision for conservative conduct. He was already completing ten days of piperacillin / tazobactam and so after evaluation with the infectious disease department, we opted to start ceftriaxone with central nervous system dose (2 g every 12 hours). Methylprednisolone was replaced by dexamethasone 2 mg every 8 hours and an assessment by the otolaryngology team was requested. Nasofibroscopy was then performed. Wide septal destruction with multiple crusts in the rhinopharynx was observed, but no fistula in which direct surgical repair could be performed was identified.

Cerebral abscess is an infection that can occur contiguously to a source of microorganisms, and usually when it occurs for this reason, it is a single abscess adjacent to the initial injury. The initial source may be previous surgery, or an dental, otological or paranasal sinus infectious disease. It can also occur by hematogenous route, especially in cases of endocarditis, and so there are multiple different abscesses, which affect the sites of vascular territories at their limits and the area between white matter and gray matter. The main risk factor is immunosuppression, and our patient had more than one factor to be immunosuppressed: drug abuse, malnutrition, and chronic corticosteroid use.

In the management of brain abscesses a surgical approach may be necessary, usually when it reaches a size greater than or equal to 2.5 cm. Surgical approach may be performed with guided aspiration or surgical excision. Excision has been less indicated, being reserved for upper fossa abscesses, which are usually single, very shallow and well circumscribed or for multiloculated abscesses in which multiple aspirations could be required to achieve the goal of surgery. For brainstem abscesses, as was the case, the preferred management is aspiration followed by antimicrobial therapy or, in minor abscesses, exclusive conservative treatment, which includes only antibiotic therapy and other medications as needed. Antimicrobial therapy is typically prolonged, so treatment of four to eight weeks may be required. In cases of surgical approach there are reports of slightly shorter therapy, from three to four weeks.

In all causes, the most common agents are *Streptococcus* and *Staphylococcus*, and anaerobes, especially in oral cavity lesions. Empirically, the initial choice of antibiotic therapy for treatment is 3rd generation cephalosporin associated with metronidazole, and vancomycin when a staphylococcal infection is suspected. Corticosteroids are not routinely done, but may help in some cases, especially when there is symptomatic edema, as in the case of the patient who had significant surrounding edema. Anticonvulsants can be used if the focus of this lesion causes epileptic seizures.¹

There was initial improvement of this patient with antibiotic therapy (he was eating more and gaining weight), but after ten days he had a significant worsening of the neck pain, progressing in a few hours with irradiation of to the frontal region, associated with photophobia, nausea and inappetence. At that moment, he was restricted to the bed because of pain, unable to lift even the cephalic segment. In mobilization, the patient reported severe pain, with neck stiffness on physical examination. Despite the significant worsening of pain, he kept stable vital signs stable, he was alert and well oriented, with no further change in strength and reflexes, maintaining the hemiparesis and hypoesthesia he already had. Pupils were isochoric and photoreactive, with preserved eye motricity, and facial movements

were preserved. But then there was the emergence of neck stiffness. Any suspicions right now?

Audience: Meningitis or bleeding?

Fabricio Neves (rheumatologist): Meningitis, possibly bacterial. He already had a brain abscess, was treating conservatively, the infectious process could spread, wouldn't it? I would think about that in the first place. It may also be a subarachnoid hemorrhage, with meningeal irritation and headache. I would think about that second.

Mayara Moraes (resident in neurology): With this clinical worsening, a new cranial tomography was requested, which surprised us with the following finding: a large diffuse pneumoencephalon, predominately located in the frontal regions, determining a slight compression over the adjacent brain parenchyma. There was also a large amount of gas inside the supra and infratentorial ventricular system, characterizing pneumoventricles, forming a hydro-air level, as well as in the basal cisterns and inside the dural sac at the level of the bulbar region. Bone ulcerations appeared again, affecting the entire nasal septum, the anterior atlas arch, the end of the odontoid process of the apex, with possible solution of continuity between the nasopharynx and the medullary canal at the cranio-vertebral transition level. The brain parenchyma was attenuated within normal range, the midline was centered, and there were no foci of contrast enhancement.

Then, at this moment, a new discussion was held with the neurosurgery team and the conservative treatment approach was maintained, with the main orientation of paying attention to possible lowering of consciousness, which would be the main motivator for a surgical approach to the pneumocephalus. Despite the signs of meningism, we chose not to perform lumbar puncture because there could be complications due to intracranial hypertension. Antibiotic therapy was changed to meropenem associated with vancomycin, and it was also decided to undergo intravenous methylprednisolone pulse therapy 1g/day for three days, then to return to dexamethasone at a dose of 4 mg every 12h.

Pneumoencephalon is, by definition, a collection of air or gas in the intracranial cavity. It may have an acute course, such as this patient, of less than 72 hours, or in some cases a later course depending on the underlying cause. It can be focal or diffuse and, in most cases, it is benign, asymptomatic and spontaneously resolved. In some cases (more severe) it may have the characteristic of being

hypertensive, with mass effect on the brain, leading to signs and symptoms of intracranial hypertension.

There are two theories for its pathophysiology. The first of these is the valve mechanism: through small fissures, from oral or nasal cavity lesions or through skull base lesions, air enters when there is an increase in extracranial to intracranial pressure. Then, in the case of cough or Valsalva, the air enters, and soon after this the fistula closes, and the incoming air is entrapped, accumulating with each repetition of this process. This may be the case with this patient. The other theory is called "inverted bottle", which would occur when there is negative intracranial pressure in relation to atmospheric pressure, occurring with excessive decrease of cerebrospinal fluid, especially when there is cerebrospinal fluid fistula, or iatrogenic drainage. In this case, air intake compensates for the pressure difference, and therefore intracranial hypertension should not occur.

The most common symptom is headache, and in the most severe cases there is alteration of consciousness, which intensity and duration will depend on air volume and location, and may lead to brainstem herniation, cardiac arrest and death. The treatment will be defined according to the etiology, the severity of the neurological compromise, the extent and volume and the progression of the air collection. Usually: conservative management in asymptomatic patients without mass effect, and surgical treatment when there is mass effect and intracranial hypertension, when there is a correctable laceration of the dura mater, or when it is possible to correct another skull base defect.

Conservative treatment, such as the one instituted for this patient, is based on absolute rest in the supine position and to avoid maneuvers that increase intracranial pressure (one of the measures is the use of laxatives such as lactulose to avoid straining in bowel movement). Proper analgesia is critical. Systemic antibiotic therapy, in suspected meningitis or oral/nasal cavity injury. Anticonvulsants when necessary. It is important to avoid hyperthermia and to make adequate electrolyte balance.²⁻³

In the first four days, our patient still presented increase in pneumocephalus size, but always keeping a stable level of consciousness and neurological examination was always unchanged. It is worth mentioning that the use of high doses of morphine was necessary throughout the patient's hospitalization, especially during this period.

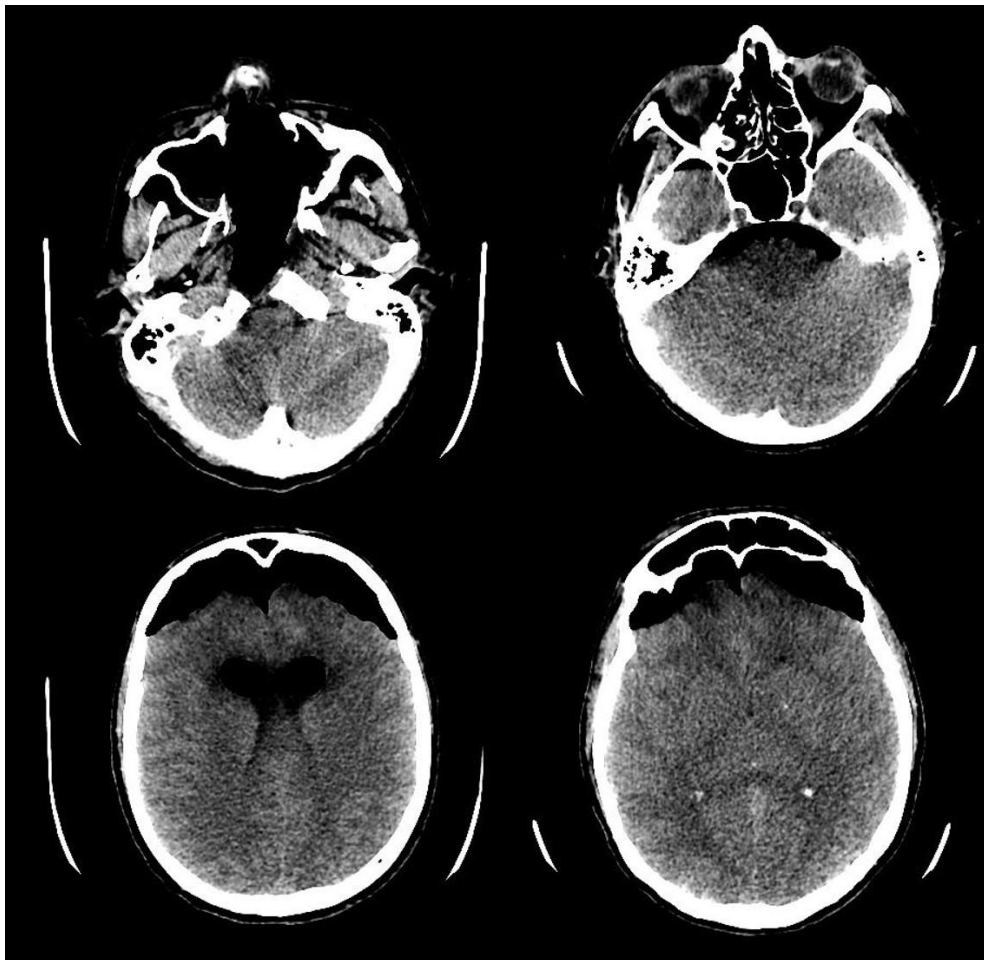


Figure 2. Cranial computed tomography showing extensive destruction of the bony structures of the face, compromising the posterior wall of the oropharynx (upper left), and the consequent pneumoencephalon. The aspect in the image below, on the right, is known as the “Mount Fuji sign” due to the similarity with the profile of this mountain.

From then on, there was gradually a decrease in pain, which was followed by a reduction in the pneumoencephalus until its complete disappearance on CT scans of the skull. Along the next weeks he gained weight, raised the head of the bed and walking with the help of his wife in the corridor. The last imaging examination at this hospitalization, again an MRI after 42 days of meropenem and vancomycin antibiotic therapy, reveals complete disappearance of both the pneumoencephalon and the abscess in the bulb, and the reconstitution of the rhinopharynx posterior wall tissues. His serum C-reactive protein is normal at this time (1.2 mg / l).

Céline Schveri (resident in rheumatology): And now we return to the differential diagnosis of the underlying disease. The major difficulty when dealing with this destructive lesion of the face is to differentiate between the destructive cocaine-induced lesion and a primary vasculitis.

The most commonly used nomenclature in the literature for the first hypothesis is “Cocaine-Induced Midline Destructive Injury” (CIMDL). The clinical symptoms of cocaine injury and GPA are similar, but CIMDL tends to be proportionally more localized, while changes in GPA are more often expected in other systems, with pulmonary and renal impairment as well. Many articles have reported that palate perforation should be considered as a marker of CIMDL, because this injury would not appear in GPA. And the destructive midline

lesions that are generated by cocaine are usually locally more severe than those caused by vasculitis. On the other hand, although GPA is usually richer in systemic manifestations, there are limited forms of the disease that can be confined to the upper respiratory tract (but usually affecting the orbits and eye).⁴ Otherwise, patients with cocaine-induced disease may also have signs of systemic vasculitis, including purpura and glomerulonephritis. These systemic findings have been attributed to the presence of levamisole (an immunostimulatory agent) as an adulterant added to cocaine.⁵

In pathologic examination there are many findings that are similar in the two diseases, such as mixed inflammatory infiltrates, or even the presence of microabscesses in the vascular walls, vasculitis and fibrinoid necrosis. For cocaine-induced injury, there would be no specific findings. But the presence of vascular alterations with granulomas with giant cells indicates the presence of GPA.

In addition to clinical and pathology, we have serology to contribute to the diagnosis. The problem is that ANCA may be positive in GPA, but may also be positive in cocaine-induced injury. And then answering the previous question: Studies show that anti-myeloperoxidase and anti-proteinase 3 are present in cocaine-induced lesions in many cases, reaching 100% of patients in one of the series. What gives us a chance to differentiate the two entities

serologically would be a specific antibody called anti-elastase, not yet routinely performed in clinical analysis laboratories.⁶

The importance of making this differential diagnosis is to allow adequate therapy, because in cocaine injury discontinuing the drug use will be the basis of treatment; but in the face of primary vasculitis, aggressive immunosuppressive therapy must be instituted. This therapy consists of two phases. First, an induction phase, where the goal is to quickly lead to remission of the disease. It usually lasts 3 to 6 months, depending on the clinical response, but it is not uncommon to extend up to 12 months of treatment. It is composed of high dose corticosteroids and an immunosuppressive agent, being the first choice cyclophosphamide or rituximab. Then there is the maintenance phase to prevent relapse, usually with long-term use of azathioprine or methotrexate, which may be associated with low dose prednisone.⁷

Audience: At no time was the biopsy repeated or the patient surgically approached, which I would consider important. And is his diagnosis vasculitis or not? That would change the treatment.

Céline Schweri (resident in rheumatology): His diagnosis now is cocaine-induced midline destructive injury. Clinical, radiological, and laboratory improvement with CRP normalization and tissue reconstitution were primarily due to antimicrobial treatment and cocaine abstinence and would not occur without intensive immunosuppression if he had GPA.

Fabricio Neves (rheumatologist): On the other hand, this disease also has an inflammatory and autoimmune basis. Millions of people use cocaine in the world and only a few develop an aggressive disease such as this, in which there are clinical and serological manifestations of autoimmunity. This suggests that CIMDL is not merely a direct toxic action of cocaine. Some people, predisposed for some reason (genetics, epigenetics, etc.), when exposed to cocaine develop a specific autoimmune disease that does not yet have a better name. It resembles GPA, and its flares may actually been minimized with the use of corticosteroids. But this disease is not GPA and should not receive continuous immunosuppression. It is probably a form of autoimmune disease whose flares can be prevented by avoiding exposure to the triggering agent, which in this case is cocaine. This is interesting but not a new concept: rheumatic fever is another autoimmune disease that works like this, we prevent its flares by preventing patient exposure to streptococci. Perhaps if we knew the triggering agents of other autoimmune diseases, they could be treated definitively by eliminating exposure to these agents rather than the continuous immunosuppression we use nowadays.

Our patient is discharged today, with referral for treatment for chemical dependence, and he did not use cocaine throughout the whole hospitalization period. The tissues of his rhinopharynx and his paranasal sinuses are probably healing. If this patient inhales cocaine again, the phenomenon will recur and may be the last time for him. Therefore, the most important measure to preserve his life, rather than corrective surgery for the alleged fistula that brought bacteria to his brainstem or the use of corticosteroids in his next flare of disease, would be to keep him permanently away from cocaine.

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