Sinogenic intracranial complications
is adalimumab a culprit?
Kofoed, Mikkel Seremet; Fisker, Niels; Christensen, Anne Estmann; Kjeldsen, Anette Drøhse

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Sinogenic Intracranial Complications, Is Adalimumab a Culprit?

Summary
We present two 11-year-old girls with chronic recurrent multifocal osteomyelitis (CRMO), treated with adalimumab. Both developed severe intracranial complications to sinusitis.

Patient 1 had been treated with adalimumab for 15 months when she developed acute sinusitis complicated by an orbital abscess, forehead swelling, a subdural empyema, and osteomyelitis of the frontal bone. She was treated with a rhino- and neurosurgical approach with intravenous (IV) antibiotics.

Patient 2 had been in adalimumab treatment for ten weeks. Adalimumab was discontinued eight weeks prior to developing subdural empyema and subcortical abscesses in combination with sinusitis. She was treated with endoscopic sinus surgery and IV antibiotics.

Both patients had developed psoriasis and episodes of infection during treatment. They were non-septic and had low fever upon presentation. None of the patients suffered any long-term neurological sequelae.

The immunosuppressive treatment with adalimumab is considered to be the culprit of the sinogenic intracranial complications in our cases.
Background

Acute bacterial sinusitis is a common disease with very low morbidity,[1] but in rare cases, infections from a paranasal sinus may spread within the boundaries of the skull.

The introduction of antibiotics has significantly decreased the incidence of intracranial complications,[2] and radiological imaging has made recognition and surgical treatment much easier.[3] Why some patients suffer from severe complications to sinusitis, while the majority experience event-free recovery is not always fully understood.

We present two girls with chronic recurrent multifocal osteomyelitis (CRMO), that to our findings are the first cases reported with sinogenic intracranial complications after treatment with adalimumab.

Adalimumab is an anti-TNF humanized monoclonal antibody,[4] the use of which has revolutionized the treatment of a range of inflammatory and autoimmune diseases. Although adalimumab has an immunosuppressive effect, and studies have shown an increased risk of serious infections in patients whilst in treatment,[5] adalimumab is still considered effective and safe.[4]

CRMO is an autoinflammatory bone disorder with multifocal sterile osteomyelitis lesions.[6] The incidence is highest among children and adolescents, with a preponderance among girls.[7] The presentation of CRMO varies greatly and can be anything from mild bone pain and local swelling to severe pain and systemic reactions with fractures of the affected sites.[6] The course of the disease is highly affected by the recurrent nature of CRMO with remissions and relapses.[6]

The condition was initially considered to be of limited duration and severity, but newly published studies of large cohorts contradict this and describe how a large number of patients have chronic pain and a severe impact on quality of life.[8] CRMO is also associated with a higher incidence of other autoinflammatory diseases like psoriasis and chronic inflammatory bowel disease.[8]

The optimal therapy for chronic nonbacterial osteomyelitis is not known. First-line treatment is considered to be non-steroidal-antiinflammatory-drug (NSAID), sometimes in combination with glucocorticoid for a limited duration. As second-line treatment, methotrexate, anti-TNF treatment and the bisphosphonate drug pamidronate have shown to be effective.[6]
Case presentation

Case 1

At the age of nine, patient 1 presented with localised pain and swelling of her lower leg. Sites of inflammation were seen in both the distal part of tibia and fibula and in the talus on MRI. CRMO was diagnosed and anti-inflammatory treatment was initiated. Prednisolone of short duration in combination with NSAID was unable to control the inflammation, and methotrexate was added for 4 months without any change. The girl was unable to run and had daily pain leading to a switch to anti-TNF treatment with etanercept. A whole body MRI was performed because of worsening of the symptoms, after 3 months of treatment. Multifocal inflammation in the sacrum and in the tibia, the fibula and the talus bilaterally was observed, no involvement of the vertebra has been observed. Remission was achieved on mono therapy of adalimumab 40 mg subcutaneously biweekly. Psoriasis, acne and episodes of skin infection developed during treatment.

Adalimumab treatment had lasted for one year and three months when she developed sinusitis and a subperiosteal orbital abscess while on vacation abroad. Adalimumab was discontinued, and appropriate surgical intervention of the sinuses and the orbital abscess was performed in combination with antibiotic treatment (amoxicillin/clavulanate). After two weeks of hospitalization abroad, the patient was discharged.

One day after discharge ("day 1" of the chronology used in this case report) the patient presented at our hospital with fever, headache, and nasal congestion, together with a fluctuating indolent forehead swelling and impaired colour vision of the affected eye.

Acute CT scan showed no signs of orbital abscess or intracranial complications, Figure 1 – Scan 1: Day 7. The fever and nasal congestion responded well to antibiotic treatment and were gone by discharge on day 17.

The forehead swelling and headache persisted and upon clinical examination on day 24, bilateral papilledema was observed. Contrast-enhanced computed tomography (ceCT) showed a 2x1.5x8 cm contrast enhanced left sided mediofrontal parafalcine empyema, Figure 1 - Scan 2: Day 24, and osteomyelitis lesions of the frontal bone extending down to the nasal bone and right orbital roof and signs of pansinusitis.

A stealth guided burr hole aspiration of the empyema and functional endoscopic sinus surgery (FESS) on both of the ethmoidal and frontal sinuses were performed. Antibiotic treatment with metronidazole, ceftriaxone, and benzylpenicillin was initiated intravenously.

Subsequent scans showed resolved intracranial suppurations, together with a slow but steady improvement in the osteomyelitis. The patient was discharged on day 62, and antibiotics were discontinued by day 66, Figure 2.

On day 112, the patient was admitted with a recurrence of the orbital abscess, and slight forehead swelling. The orbital abscess was drained, and a fistulation between the right orbit and sinus frontalis was found. CT scan identified severe osteomyelitis lesions of the frontal bone, Figure 1 – Scan 3: Day 112. Endoscopic nasal surgery with trephination of sinus frontalis and a bone biopsy was done. Long-term IV antibiotics with ceftriaxone and metronidazole were reinstituted.

Investigations

- *Streptococcus* of the anginosus group was found by 16s rRNA amplification and sequencing of aspiration material from the subdural parafalcine empyema.

- *Staphylococcus epidermidis, Streptococcus mitis*, and *Corynebacterium* were identified by cultivation of bone biopsy from the frontal bone.

- Histological evaluation of bony material from the frontal bone showed inflammation typical for osteomyelitis.
**Differential diagnosis**
Patient 1 developed severe osteomyelitis of the frontal bone that responded, although very slowly, to antibiotic treatment. Because of the slow response, it has been thoroughly discussed whether it could be a manifestation of CRMO.
It seemed unlikely, as CRMO almost never affects the neurocranium,[6,7,9,10] Initial examinations demonstrated several microorganisms in both bone aspiration and bone biopsy. Furthermore, every relapse occurred following cessation of antibiotic therapy and taken together, these findings, in our opinion, ruled out an atypical manifestation of CRMO.[7]

**Outcome and follow-up**
On day 269 the subdural empyema and sinusitis were considered fully treated. Upon follow-up two months after the discontinuation of antibiotic treatment, day 434, no relapse of sinusitis was described. Forehead swelling was not present, but CT scan still showed active osteomyelitis of the frontal bone.

Seven months after the discontinuation of the antibiotic treatment, on day 604, the patient was admitted, once again with an indolent fluctuating forehead swelling. Both CT and MRI showed osteomyelitis lesions in progression but no signs of recurrence of intracranial suppurations (Figure 1 – Scan 4: Day 604). Antibiotic treatment was resumed.
Antibiotic treatment is still on going as depicted in Figure 2. Removal of the affected part of the frontal bone and a replacement with titanium is planned if the osteomyelitis shows no response, or worsens. The patient has suffered no short- or long-term neurological deficits but is still affected by mild headaches. Besides NSAID she has not received any treatment for CRMO while in treatment for intracranial complications.
Case 2

Patient 2 had increasing pain from her legs, feet, arm and clavicle during 18 months. At admission she was unable to walk, using a wheelchair. Multiple inflammation sites were localised in both clavicles, the right humerus, the lumbar spine, the sacrum, the ileii, both femora, both tibia and metatarsal bones in both feet on MRI. When CRMO was diagnosed she was 10 years old. Short periods of pain relief were accomplished using NSAID and prednisolone. Methotrexate was added after 4 weeks and due to continued symptoms, anti-TNF treatment with etanercept was started. After 5 months in remission, renewed symptoms appeared in combination with dermal symptoms of psoriasis and pustulosis palmoplantaris. Etanercept was replaced with adalimumab given subcutaneously biweekly. Remission was achieved for the osteitis. During the next 10 weeks of treatment complaints of stomach ache and recurrent episodes of otitis media occurred together with the report of possible allergic rhinitis. Adalimumab treatment was stopped and the patient continued on a low dose of methotrexate (10 mg weekly).

She was admitted after a sudden “temporal lobe like” seizure 8 weeks later. The patient reported influenza-like symptoms, with nasal congestion, headache, and vomiting five days before the seizure and an intermittent swelling below the right eye. Upon admission to the hospital, the clinical presentation was completely normal apart from low fever.

Pansinusitis but no intracranial complications were demonstrated on a CT scan. Discrete pleocytosis (27x10E6/L) in the cerebrospinal fluid was the only marker of possible intracranial infection. Antibiotic treatment with ceftriaxone and metronidazole was initiated intravenously. Methotrexate was discontinued upon admission.

Following clinical deterioration and another seizure, a right-sided frontal subdural empyema, adjacent cerebritis and meningeal enhancement in addition to small subcortical abscesses were identified on contrast-enhanced MRI and ceCT (Figure 3 - Scan 2 and 3: Day 11).

FESS was performed on the involved sinuses but no indication for surgical intervention on the intracranial suppurations was found. Adding benzylpenicillin intensified the antibiotic treatment. (Figure 4)

Investigations

- *Streptococcus* of the anginosus group was found by 16s rRNA amplification and sequencing on mucus from the paranasal sinuses.
- CSF analysis was sterile.
- Osteomyelitis was not evident in the frontal bone by histological evaluation.

Outcome and follow-up

Regression of the intracranial suppurations was shown on subsequent MRI (Figure 3 - Scan 4: Day 68). Additional endoscopic sinus surgery was done due to persistent findings of sinusitis despite treatment. The patient became sensitized towards ceftriaxone and treatment was changed to meropenem. At discharge oral clindamycin was initiated (Figure 4).

No signs of intracranial suppurations or mucosal swelling in the paranasal sinuses were found on a recent scan. Antibiotic treatment was discontinued on day 244. The patient has suffered no short- or long-term neurological deficits. The patient received NSAID for her CRMO during treatment.
Discussion
Paediatric sinogenic intracranial complications
Sinogenic intracranial complications occur when an infection from the paranasal sinuses spread within the boundaries of the skull. It is thought to be primarily by hematogenous transmission through the valveless diploic veins. Direct spread of infection by osteomyelitis is also seen but is less common.[2]

The frontal sinus is most often seen as the origin of spread. This is thought to be because of an abundance of diploic veins, a thin posterior wall, a delayed but rapid development of the sinus in early adolescents and because of the frequent involvement in sinusitis.[2]

Sinogenic intracranial complications include the most common, subdural empyema (49%), then epidural abscesses (36%), cerebral abscesses (21%), and meningitis (10%). Cavernous sinus thrombosis (4%), frontal bone osteomyelitis (3%) and encephalitis (1%) are also seen.[11]

Sinogenic intracranial complications have been reported to be present in 0.1% of children presenting to an emergency department with acute bacterial sinusitis.[1] The incidence peaks at early adolescence, and is most commonly seen in males.[11,12] An increased prevalence of asthma in patients having intracranial complications to sinusitis has proposed a correlation with asthma (none of our patients had asthma).[12] Seasonal clustering with a higher incidence in winter, have been observed.[12]

Presentation
The presentation of sinogenic intracranial complications is often mild and unspecific. Headaches (84%) and fever (74%) are the most common symptoms. But nausea and vomiting (38%), neurological deficits (38%), mental state change (32%), symptoms of sinusitis (28%), and seizures (18%) are also reported.[11]

The traditional triad of symptoms associated with intracranial suppurations, fever, headache, and focal neurological deficits, are only present in 13% of children with intracranial complications.[13] Subdural empyema presents in a more fulminant manner, with a higher percentage of neurological deficits.[11]

Imaging
Contrast-enhanced MRI and CT are considered to be complementary examinations when intracranial complications to sinusitis are suspected.[14]

CT lacks sensitivity towards intracranial suppurations but depicts the anatomic detail of the paranasal sinuses and bony formations better.[14] It is also more easily acquired with no need for sedation.

Contrast-enhanced MRI differentiates soft-tissue mass better[14] and has a higher sensitivity towards intracranial suppurations.[3] MRI with diffusion-weighted imaging (DWI) is very sensitive to detecting pus formation.[15,16] Fluid-attenuated inversion recovery (FLAIR) is helpful in detecting oedema, early abscess formation, and meningeal involvement.[15,17]

Both MRI of the head and CT of the paranasal sinuses and orbits are frequently needed in the pre-surgical assessment of sinusitis and the intracranial extensions.[14,15] A higher index of suspicion should be obtained towards immunocompromised patients, with MRI as the favoured investigation.[14] If MRI is not to be obtained, ceCT is considered the optimal radiological examination of the acute patient.[14]
Treatment

Surgical
The core of surgical treatment is an early and aggressive approach, with a combined neurosurgical removal of the suppuration and endoscopic sinus surgery.[11,18,19]

The most favourable surgical treatment is yet to be established.[11] Smaller studies have demonstrated successful operations of epidural abscesses with an endoscopic transnasal approach, while subdural empyema, to a larger extent, needs craniotomy or burr hole aspiration.[19]
The specific role of endoscopic sinus surgery and its impact on survival and morbidity is also yet to be demonstrated.[11,19,20]

Subdural empyemas are associated with more procedures and worse outcome when compared to epidural abscesses.[11,19] Immunocompromised patients also have a worse outcome.[13]

Antibiotic
Streptococcus of the anginosus group previously referred to as the milleri group, consist of S. anginosus, S. intermedius, and S. constellatus. They are the most common causative microorganisms related to sinogenic intracranial complications.[11,13,19,21]

IV ceftriaxone and metronidazole are the recommended empiric antibiotic treatment.[13,22]
Meropenem is recommended in immunocompromised patients, as it gives a broader pathogen cover.[13]

The duration of antibiotic treatment is highly debatable. Recommendations on a minimum of six weeks, with an IV treatment of one to three weeks, have been proposed.[13] Often, including in our cases, treatment should last much longer.
The use of oral antibiotics against intracranial suppurations is also discussed vigorously.
An appropriate oral regimen, subsequent to IV treatment, is amoxicillin/clavulanate.[13]
Any change in IV antibiotics, from IV to peroral, should be guided by significant improvement in the patient’s clinical condition and inflammatory markers.[13]

Anti-TNF treatment
Tumor necrosis factor alpha (TNF-alpha) is a proinflammatory cytokine and is part of the acute phase response. It exerts multiple effects on the immune system by binding to one of the two types of receptors (TNFR1 and TNFR2). In certain autoinflammatory diseases dysregulation of TNF-alpha is an important parameter in the inflammatory process.[23]
Some Tumor necrosis factor alpha antagonists specifically bind to TNF-alpha-receptors and prevent the stimulation of immunological target cells and development of autoimmune inflammation. Adalimumab is one of these TNF-alpha inhibitors and has a half-life of 10-20 days.[23] Since Adalimumab binds to TNF-alpha receptor it is not known, if the plasma half-life is actually the true half-life of the drug. According to the manufacturer’s Summary of Product Characteristics patients in treatment with Adalimumab should be closely monitored for infection up to 4 months after discontinuation since the elimination might be this long.[24]
Several studies have observed that patients can be in remission, or in low disease activity, for up to three years after discontinuing TNF-alpha inhibitor treatment.[25,26] Whether this is due to drug activity or the nature of the disease is not known.
Our cases
Both of our cases were non-septic and had low fever with a good activity level upon presentation. The first patient presented with fever, headache and nasal congestion that quickly subsided on antibiotics leaving only headaches when the diagnosis was made. The second patient presented with a temporal lobe like seizure but with an otherwise normal clinical condition and activity level with only a slight fever. Our cases underline the important lesson that, sinogenic intracranial complications present with few symptoms in the paediatric population.

Psoriasis is known to be associated with CRMO. Development of psoriasis is also described as a possible adverse event in patients treated with Anti-TNF. Both of our patients developed psoriasis during anti-TNF treatment. Whether this was due to the nature of the disease or caused by the treatment is not known. Other symptoms of possible side effects and markers of risks were the development in both children of infectious episodes of recurrent otitis media and skin abscesses, respectively.

We cannot predict with certainty the duration of immunosuppression after discontinuing Adalimumab. Chronic sinusitis developed already during treatment with adalimumab in patient 2, and even though administration of the drug was stopped 8 weeks prior to the development of intracranial complications, it might still have affected the inflammatory process.

Conclusion
An association between anti-TNF treatment with adalimumab, and recurrent sinusitis has already been proposed,[29,30] but the true relationship is yet to be established. A prospective study, investigating the development of sinonasal symptoms and possible complications in children treated with anti-TNF, would give further information.
This case report wants to increase the awareness of the possible risk of sinogenic intracranial suppurations among children treated with adalimumab.
Learning points

• Sinogenic intracranial complications are rare and present with mild and varying symptoms in the paediatric population.

• A high level of suspicion and a low threshold for CT and contrast enhanced MRI should be obtained towards children presenting with neurological deficits or symptoms of increased intracranial pressure.

• An especially high level of attention and suspicion should be given to patients in immunosuppressive treatment, due to a poorer outcome and a higher incidence of serious infections.

• The Immunosuppressive effect of adalimumab might persist up to four months after the discontinuation of the drug; patient should be monitored closely for this period of time.

• Adalimumab is considered to be the culprit of the sinogenic intracranial complications in our cases.

• Further research is needed in order to fully investigate the relationship between immunosuppressive treatment with adalimumab, sinusitis, and sinogenic intracranial complications.


Legends

Figure 1: Case 1 - Radiologic imaging – CT and MRI axial scan at parafalcin empyema level
Figure 2: Case 1 - Timeline of antibiotic therapy and surgical procedures

Figure 3: Case 2 - Radiologic imaging – CT and MRI axial scan at parafalcin empyema level
Figure 2: Case 2 - Timeline of antibiotic therapy and surgical procedures
Scan 1: Day 7 – Forehead swelling
CT showed pansinusitis

Scan 2: Day 24 – Papiledema
CeCT showed intracranial suppurations

Scan 3: Day 112 – Orbital abscess
CT showed osteomyelitis

Scan 4: Day 611 – Forehead swelling
MRI FLAIR showed osteomyelitis
Scan 1: Day 1 – Seizure CT showed pansinusitis

Scan 2: Day 11 – Second seizure CeCT showed intracranial suppurations

Scan 3: Day 11 – Second seizure MRI T2 showed intracranial suppurations

Scan 4: Day 68 – Follow-up MRI FLAIR showed remission