

Case Study

# Recurrent ethmoid mucocele with cellulitis in a patient with Pfeiffer syndrome

Anjan Nibber<sup>1</sup> and Calum Honeyman<sup>2</sup>

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Craniosynostosis, Pfeiffer syndrome, ethmoid sinusitis, periorbital cellulitis.

<sup>1</sup>Medical Sciences Division, University of Oxford, UK

<sup>2</sup>Nuffield Department of Surgical Sciences, University of Oxford, UK

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## Key Learning Points

### Calum Honeyman

Pfeiffer syndrome is one of six craniosynostosis syndromes and presents with craniosynostosis (the premature fusion of one or more calvarial sutures) and skeletal abnormalities. The aetiology of Pfeiffer syndrome is thought to be caused by mutations in the fibroblast growth factor genes *FGFR1* and *FGFR2*. The anatomical complexity of craniosynostosis syndromes means that the long-term management of patients requires a multidisciplinary team approach. Patients with craniosynostosis syndromes are predisposed to sinus infections, including sinusitis, due to structural abnormalities and iatrogenic alterations in sinus anatomy following reconstruction. In this case report, we report a 14-year-old boy with Pfeiffer syndrome who presented with periorbital cellulitis secondary to recurrent ethmoid sinusitis. To the best of our knowledge, this is the first case of ethmoid sinusitis in a patient with Pfeiffer syndrome reported in the literature.

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## 1 Background: What is Pfeiffer syndrome?

Pfeiffer syndrome is the rarest of the craniosynostosis syndromes, a group of syndromes with a genetic aetiology and which are characterised by premature calvarial suture fusion and skeletal abnormalities (Supplementary Material Table 1). The majority of Pfeiffer syndrome patients have severe pan-synostosis resulting in major calvarial distortion, raised intracranial pressure (ICP), facial abnormalities (predominantly midface hypoplasia and proptosis), and broad and deviated thumbs and great toes. Definitive diagnosis of Pfeiffer syndrome requires computed tomography (CT) imaging showing the presence of craniosynostosis, and associated physical characteristics.

Three types of Pfeiffer syndrome are described, with variable degrees of severity.<sup>1</sup> Type 1, also known as 'classic' Pfeiffer syndrome, is characterised by pan-synostosis, maxillary hypoplasia and less severe proptosis. It is usually inherited in an autosomal dominant manner, and most patients go on to live a normal life span. Type 2 is the most severe subtype and is defined by a cloverleaf-shaped skull with severe midface hypoplasia and proptosis. Type 3 is similar to type 2, but without a cloverleaf-shaped skull. Both type 2 and 3 Pfeiffer syndrome tend to occur sporadically and have a poor prognosis.

Like many of the syndromic craniosynostosis, Pfeiffer syndrome is caused by mutations of the fibroblast growth factor receptor 1 and 2 genes.<sup>2,3</sup> The clinical

consequences of these mutations are complex and may promote early osteoblast maturation and proliferation, leading to premature bone fusion.<sup>4</sup>

Early surgical intervention may reduce the risk of secondary complications in patients with craniosynostosis syndromes. As such, it is not uncommon for patients to undergo a handful of surgeries within the first few years of life. In a single-centre retrospective study, Fearon et al.<sup>5</sup> reported that the average number of operations of a Pfeiffer syndrome cohort (mean age 10) was 9.3. They reported that patients with Pfeiffer syndrome were most likely to undergo cranial vault reconstruction, maxillary advancement(s), neurosurgical operations, tracheostomy, and gastrostomy tube placement. The management of these patients is life long, as additional procedures throughout their lives may be required to correct craniofacial related complications.

## 2 Case Study - PK

### 2.1 History

PK is a 14-year-old male who presented to his local GP with a swollen right eye. Symptoms including swelling, increased pressure, and fluid production had started three days prior and progressively worsened. PK was referred with suspected periorbital or orbital cellulitis to the Craniofacial Unit at the John Radcliffe Hospital for further investigation and management.

PK has been under the care of the Craniofacial Unit

in Oxford since birth, when he was diagnosed with type 1 Pfeiffer syndrome, following an uncomplicated pregnancy. PK's medical history consists of numerous craniofacial operations including cranial vault reconstructions to correct for skull deformity and reduce the complications of high ICP, osteotomy of the maxilla and advancement, as well as procedures to ease breathing (tracheostomy) and feeding problems (percutaneous endoscopic gastrostomy in situ). PK's siblings and parents are all healthy and there is no family history of craniofacial syndromes. His parents are unrelated, and genetic testing was not reported.

PK also has a past medical history of sinus infections for which he has undergone frontal sinus drainage and endoscopic surgery of his ethmoid sinus in 2016 (discussed in further detail below). Prior to this latest presentation, PK has been in good health and excelling in school where he enjoys art and spending time with his friends and brothers.

## 2.2 Differential diagnosis and examination

Children presenting with unilateral erythematous swollen eyelids pose a medical challenge as a number of differentials must be considered, including orbital cellulitis, which is a surgical emergency. Orbital cellulitis and periorbital cellulitis can be difficult to distinguish from one another. Key distinguishing features are outlined in Table 1. Periorbital cellulitis is an infection of the soft tissue of the eye anterior to the orbital septum and is characterised by acute onset of eyelid oedema, tenderness, and erythema. It can occur at any age but is more common in the paediatric population.<sup>6</sup> It is imperative that periorbital cellulitis be differentiated from orbital cellulitis (infection of fat and ocular muscles), which is associated with more severe complications such as vision loss, brain abscesses, cavernous sinus thrombophlebitis and orbital abscesses. Most patients with periorbital swelling, and all patients with suspected orbital cellulitis must be admitted to hospital.<sup>6</sup> Additional differentials for a unilateral swollen eye to consider are herpes simplex, herpes zoster, hordeolum, and chalazion tumor.<sup>7</sup> However, as no vesicles or lid lesions were noted, these differentials were less likely.

**Table 1: Clinical Features of periorbital and orbital cellulitis**

Clinical Feature	Periorbital Cellulitis	Orbital Cellulitis
Eyelid swelling	Yes	Yes
Eye pain at rest	May be present	Yes
Pain with eye movement	No	Yes
Visual impairment	No	May be present
Ophthalmoplegia/CN palsies	No	May be present

*Adapted from Denniston and Murray<sup>8</sup>*

At presentation, observations were stable (HR; 70, BP; 117/70, Temp 37C, RR 14), GCS was 15. On initial examination, PK's eye was completely closed from the swelling, and no vesicles, or lid lesions were noted. No pain was reported at rest or on movement. There was no evidence of spreading erythema on the face, nor the presence of any leakage and pus. The lack of pain coupled with erythematous swelling of his eye lid fit closely with a diagnosis periorbital cellulitis. However, a right abducens (CN VI) palsy was noted, and as such periorbital cellulitis could not definitely be confirmed without imaging as nerve palsies are more commonly associated with orbital cellulitis. All other aspects of the neurological examination

and other systems were normal. Bloods revealed a raised CRP of 98.2, all other values were in the normal range.

## 2.3 Underlying cause

Periorbital and orbital cellulitis as complications of sinusitis are well recognised clinical entities. Sinusitis has been implicated in up to 30% and 91% of periorbital and orbital cellulitis cases, respectively.<sup>9,10</sup> Understanding how sinusitis may cause periorbital and orbital cellulitis requires an understanding of the anatomy of the orbit and paranasal sinuses.

The orbit is a cone-shaped structure, which is surrounded by four bilaterally paired paranasal air sinuses named according to the bone they are located in: frontal, ethmoid, sphenoid and maxillary. The main function of the sinuses is to humidify inspired air. Lining the sinuses is respiratory mucoperiosteum, which drains via small openings (sinus ostia) into the lateral nasal cavity. Sinusitis specifically refers to the inflammation of the mucoperiosteum.

Upper respiratory tract infections can spread to the sinuses as they are continuous with the nasal cavity. In the sinuses, viral infections can impair cilia function resulting in mucous stasis and blockage of the sinus ostia. Blockage of the sinus prevents adequate drainage and ventilation creating a breeding ground for bacteria, and subsequent sinusitis. When sinusitis is the primary cause of periorbital or orbital cellulitis, infection usually spreads from the ethmoid sinus. The ethmoid sinus is separated from the orbit by the lamina papyracea, a thin wall with many perforations for nerves and vasculature to run through. The close proximity of the structures makes it easy for infection to spread.

Sinusitis can result in the production of epithelium-lined cystic masses filled with mucous, called mucoceles. Mucoceles generally expand slowly, but when infected can enlarge rapidly, exerting pressure on sinus bones. Erosion of an ethmoid mucocele through the lamina papyracea and into the orbit can lead to periorbital and orbital cellulitis, which has shown to be mediated by prostaglandins and collagenases produced from mucoceles.<sup>11</sup>

## 2.4 Investigations

CT or MRI imaging is helpful for distinguishing periorbital from orbital cellulitis, particularly if a full eye examination is not possible. Furthermore, imaging can help deduce whether the cause is sinusitis related. Microbiology cultures are rarely performed due to the difficulty in obtaining swabs from the site of infection and the general lack of positivity of blood cultures.<sup>6</sup>

As the medical team were unable to assess PK's vision, imaging was requested. An MRI scan showed inflammation of the right eyelid, but a lack of inflammation of the extraocular muscles, confirming a diagnosis of periorbital cellulitis. An expanded ethmoid sinus (20mm) and the presence of an isolated infected ethmoid mucocele, the most likely source of infection were noted. No brain parenchymal involvement was noted. A follow up MRI revealed shrinkage of the mucocele.

## 2.5 Treatment

Recent guidelines suggest that if a definitive diagnosis of periorbital cellulitis cannot be made, patients should be started on broad-spectrum antibiotics which is the standard treatment for orbital cellulitis.<sup>6</sup> These guidelines highlight the concern for orbital cellulitis complications such as vision loss if the optic nerve is affected. Based on

these recommendations, PK was started on a course of broad-spectrum antibiotics (chloramphenicol, flucloxacillin, xylometazoline, metronidazole, ciprofloxacin (eyedrops), ceftazidime) and lower eyelid compression. After five days in hospital, PK showed marked improvement and CRP levels decreased. The swelling in his right eye had significantly reduced and he was spontaneously able to open his eye. Subsequent examination revealed normal visual acuity, and eye movements. The consensus was that PK was well enough to be discharged, and should continue taking oral antibiotics whilst his periorbital cellulitis is monitored at his local hospital.

In addition to treatment for periorbital cellulitis, treatment of sinusitis should be considered, particularly in patients with recurrent sinusitis episodes. This is to prevent complications such as mucocele production. Functional endoscopic sinus surgery (FESS) is an option for patients suffering from chronic (over 12 weeks) or recurrent sinusitis with complications, and where medical interventions (nasal spray, drainage, and antibiotic treatment) have not been successful.<sup>12</sup> In FESS, fiberoptic telescopes and CT are used to identify diseased sinuses and sinus ostia are opened, to allow for drainage. This is in contrast to conventional sinus surgery which involves the removal of mucosa lining the sinuses, as it was previously believed that following chronic inflammation the mucosa was irreversibly damaged.<sup>15</sup> The complications of both of these procedures are small.<sup>13</sup>

Following the development of a frontal sinusitis and an ethmoid mucocele in 2016, PK underwent frontal sinus drainage and FESS of his ethmoid sinus so to prevent recurrent sinusitis. Unfortunately, the technique was ineffective as PK presented with ethmoid sinusitis complications within three years.

### 3 Discussion

Interest in this case focuses around the development of periorbital cellulitis secondary to recurrent ethmoid sinusitis in a patient with Pfeiffer syndrome, and in which previous sinus surgery has failed. Whether patients with craniofacial variants or who have undergone surgery are at an increased risk of sinusitis and associated complications is unclear. To the best of our knowledge, ethmoid sinusitis infections and periorbital cellulitis, have not been previously reported in patients with Pfeiffer syndrome. One case of maxillary mucocele formation following craniofacial surgery has been reported in a patient with Pfeiffer syndrome.<sup>14</sup> However, a few cases of sinusitis in other craniosynostosis syndrome patients, predominantly Crouzon syndrome, have been reported in the literature (Table 2).

### 3.1 Sinusitis due to anatomic abnormalities

Several anatomic variants have been identified in patients that suffer from chronic and recurrent sinusitis including nasal septal deviation, concha bullosa deformity, and paradoxical curvature of the middle turbinate.<sup>21</sup> Whilst recognising that these variants are also found in healthy individuals, Drake and Rosenthal<sup>21</sup> suggest that septal deviation (which is found in many patients with midface hypoplasia) may be the cause of chronic or recurrent sinusitis in patients with craniofacial disorders. This is supported by Altintas et al.<sup>15</sup> who reported chronic bilateral maxillary, ethmoid and sphenoid sinusitis in three patients with Crouzon syndrome, with septal deviation and who had not yet undergone craniofacial surgery. However, characterization of sinus abnormalities in syndromic craniosynostosis in the literature is limited.

### 3.2 Sinusitis as a post-operative complication

More common than anatomic variants are studies reporting the development sinusitis following corrective craniofacial surgery. Sinusitis and mucoceles may develop following trauma, such as during craniofacial surgery. In their retrospective case series of seven patients with craniofacial abnormalities, Woodworth et al.<sup>20</sup> highlighted that whilst patients with craniofacial syndromes may have congenital changes to their sinus anatomy which predispose them to infection, anatomical changes following corrective craniofacial surgery may exacerbate the problem. The authors reported two patients diagnosed with Crouzon syndrome, who developed chronic sinusitis following corrective surgery. One patient developed frontal mucoceles and septal perforation, and the second patient developed septal perforation without the development of mucoceles. Analysis of the ethmoid sinuses showed bilateral dehiscence of the lamina. The authors highlighted the importance of long-term surveillance as mucoceles may form many years after surgery. In both Crouzon patients (and in the remainder of the five patients with other craniofacial anomalies but without a diagnosis of craniosynostosis) endoscopic surgery was performed and at follow up (mean time 15 months), no complications had been reported.

The timeframe of development of sinusitis and mucoceles is highly variable. For example, Coeugnet et al.<sup>17</sup> reported the development of maxillary sinusitis in one patient with Crouzon syndrome and one with Apert syndrome within seven days of craniofacial surgery. Tatla et al.<sup>19</sup>, reported on a 12-year-old boy with Crouzon syndrome that developed frontoethmoidal mucoceles 18-months post-surgery. There are also reports of sinusitis complications occurring as long as 15- and 19-years post-

**Table 2\*: Summary of sinusitis cases reported in craniosynostosis syndromes**

Author	Type of craniosynostosis syndrome	Patients reported with sinusitis	Findings
Altintas et al. <sup>15</sup>	Crouzon syndrome	3	Chronic bilateral ethmoid, maxillary, and sphenoid sinusitis was noted in three patients who had not undergone craniofacial surgery.
Brown et al. <sup>16</sup>	Apert syndrome	1	Development of frontal sinus mucocele 19 years following craniofacial surgery.
Coeugnet et al. <sup>17</sup>	Crouzon syndrome, Apert syndrome	2	Seven days following craniofacial surgery, two patients developed maxillary sinusitis, which recovered after removal of one K wire.
Nakae et al. <sup>18</sup>	Crouzon syndrome	1	Patient developed meningitis and recurrent otitis media and sphenoid and ethmoid sinusitis 10 years following craniofacial surgery.
Patel et al. <sup>14</sup>	Pfeiffer syndrome	1	Maxillary mucoceles with associated proptosis were found 15 years following craniofacial surgery.
Tatla et al. <sup>19</sup>	Crouzon syndrome	1	Development of frontal and ethmoid mucocele 18 months following craniofacial surgery.
Woodworth et al. <sup>20</sup>	Crouzon syndrome	2	Following bifrontal craniotomies, one patient developed bilateral frontal mucoceles and septal perforation and one patient had septal perforation without mucocele production.

\*PubMed and SCOPUS databases were searched using the following terms: 'Pfeiffer syndrome', 'craniosynostosis syndrome' AND 'sinusitis', 'periorbital cellulitis', 'mucocele'.

surgery in a Pfeiffer syndrome and Apert syndrome patient, respectively.<sup>14,16</sup>

In addition to sinusitis, craniofacial surgery has also been implicated in the development of other infections. Nakae et al.<sup>18</sup> reported a case of a 29-year-old woman who following craniofacial surgeries in childhood developed meningitis at 19 and again at 23, the latter time following the development of otitis media and sinusitis (sphenoid and ethmoid).

### 3.3 Sinusitis as a complication of sinus surgery

This case raises the question as to whether FESS is indeed an effective treatment for sinusitis. FESS has become an established surgical strategy for the treatment of recurrent and chronic sinusitis and yet there is limited data available showing its efficacy. Two Cochrane reviews concluded that whilst FESS is a safe procedure for chronic and recurrent sinusitis, the studies investigating the effectiveness of FESS are of low quality and therefore there is no evidence to confer benefit over medical interventions.<sup>15,22</sup> Mucocele recurrence rates following surgery vary among sources, with some studies reporting rates close to 0% and others nearer 10%.<sup>23,24</sup>

In their retrospective review, Busaba and Salman<sup>25</sup> described 14 patients who developed ethmoid mucoceles one to 13 years after FESS. As mentioned previously, mucoceles are generally slow growing but may expand rapidly if there is secondary infection. Surgeons should be aware of the potential complications of mucocele development which may potentially occur many years after surgery. Whether the complex anatomy of craniosynostosis syndrome patients makes an endoscopic approach less effective, remains to be elucidated. An open approach procedure (Caldwell-Luc), which allows for the entire sinus to be evacuated was found to be effective in a 36-year old Pfeiffer syndrome patient who 15 years post-maxillary advancement surgery developed maxillary mucoceles.<sup>14</sup> An open approach was also found to be effective in the treatment of frontal sinus mucocele development in a 43-year-old man with Apert syndrome, 19 years after maxillary advancement surgery. As such, a traditional approach may need to be considered for patients with a craniosynostosis syndrome and a history of recurrent sinusitis.

A final consideration, albeit small is the risk of atrophic rhinitis following sinus surgery. Atrophic rhinitis is an uncommon form sinusitis which results in progressive atrophy of the nasal mucosa, and paradoxical mucous production. It can be due to repeated sinonasal trauma from surgeries, which as discussed above can induce the development of mucoceles and by extension sinusitis.<sup>26</sup>

## 4 Conclusions

The true incidence of sinusitis and its complications in craniosynostosis syndromes is not known, but anatomical variation is considered to be a serious consideration for these patients. Evidence of associations have predominantly focused on the development of sinusitis following craniofacial surgeries in Crouzon syndrome patients. The production of mucoceles, potentially many years later may be a serious post-operative concern, which craniofacial surgeons and ophthalmologists should be more aware of.

The complex anatomy of Pfeiffer syndrome patients adds a layer of complexity in the treatment of sinusitis and periorbital cellulitis and indeed many other pathologies. PK will need to be under the care of a multi-disciplinary team for the rest of his life to ensure that any complications are treated by doctors and surgeons familiar with his medical history. This report documents the second case of a Pfeiffer syndrome patient with mucocele development following craniofacial surgery, and the first case of a Pfeiffer syndrome patient presenting with periorbital cellulitis secondary to an ethmoid mucocele.

### Conflicts of interest

None.

### Funding

None.

### Consent

The patient and the guardian of the patient consented for the publication of this case study.

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### Supplementary Material Table 1: Summary of craniosynostosis syndromes (adapted from Buchanan et al.<sup>27</sup>)

Craniosynostosis syndrome	Incidence	Aetiology	Suture synostosis	Associated features
Apert syndrome	1 in 70,000	FGFR2 mutation (autosomal dominant, sporadic)	Multiple suture synostoses. Usually always coronal sutures and later lambdoid	Acrosyndactyly of the hands, mid-face hypoplasia, upper limb anomalies
Crouzon syndrome	1 in 70,000	FGFR2 mutation (infrequently reported mutation in FGFR3)	Bicoronal synostosis	Mid-facial hypoplasia, exorbitism, obstructive sleep apnoea
Pfeiffer syndrome	1 in 120,000	FGFR1 or FGFR2 mutation (autosomal dominant, sporadic)	Pan-synostosis	Mid-face hypoplasia. Raised intracranial pressure, proptosis, obstructive sleep apnoea. Large thumbs and toes
Muenke syndrome	1 in 30,000	FGFR3 mutation (autosomal dominant)	Uni- or bicoronal synostoses	Variable infra-temporal bulging
Cranial front-nasal dysplasia	1 in 120,000	EFNB1 (X Chromosome)	Coronal synostosis	Hypertelorism, short nose, high palate, clavicles and shoulder girdle are hypoplastic
Saethre-Chotzen syndrome	1 in 80,000	TWIST1 gene (autosomal dominant)	Variable, most frequently bicoronal	Low hairline, eyelid ptosis, small ears, mild syndactyly of the fingers

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