Caso clinico

Case reports

What is hiding behind bubbles of air? An unusual *Streptococcus pyogenes* meningitis

Cosa si nasconde dietro le bolle d'aria? Un'inusuale meningite da Streptococcus pyogenes

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INTRODUCTION

Group A Streptococcus (GAS) infections have traditionally been most common in the young and in the elderly [1, 2]. GAS frequently colonizes the oropharynx and is a common cause of acute pharyngotonsillitis in 32.3% of pediatric patients, with an incidence of 40.4% in children, 24.7% among the adolescents and 13.1% among adults [2]. Although an increase in invasive *Streptococcus pyogenes* disease has been reported during the 1990s and into the 2000s, bacterial meningitis remains fairly uncommon in adults, representing less than 1-2% of invasive GAS disease [1]. Nonetheless, sporadic cases can occur and may have a fulminating course with high mortality (27%) and relevant neurological sequelae (43%) [3]. Here we report on a rare case of otogenic *S. pyogenes* meningitis with pneumocephalus, where the MRI of the brain revealed a partial thrombosis of the right transverse sinus and initial subdural cerebral empyema.

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CASE REPORT

A previously healthy 36-year-old female was admitted to the emergency department (ED) of our hospital three days after the onset of earache and otorrhoea. In the morning of the day of admission the patient was found unconscious. Upon arrival at the ED she was confused and had bitten her tongue. During physical examination it was found that she was afebrile, had an oxygen saturation of 96% on room air, a blood pressure of 120/85 mmHg and a hearth rate of 120 beats per minute. She weighed 74 kg and was 168 cm tall. Her biochemical data was found to be within normal limits, apart from a raised white cell count of 30.93x103/µl (neutrophil 93.8%, lymphocyte 0.9%) and an increased CRP of 21.2 mg/dl, indicating a proinflammatory state. The CT scan of the brain showed cerebral edema, right sided mastoiditis and pneumocephalus (Figure 1, A-C). Microbiological cultures were obtained. A lumbar puncture however was avoided because of the presence of cerebral edema on the brain CT scan and the comatose state of the patient which was due to generalized tonic-clonic seizure. The patient was treated empirically with cefotaxime (2 g, every four hours, 12 g/24

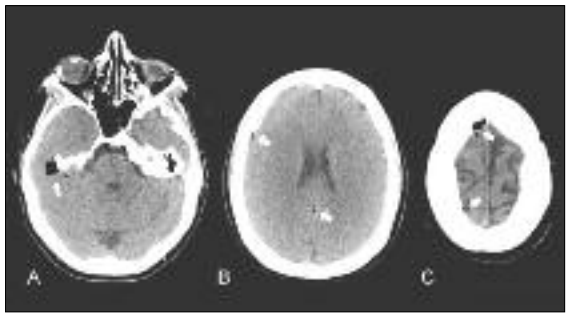

Figure 1 - CT of the brain showing pneumocephalus (white arrows).

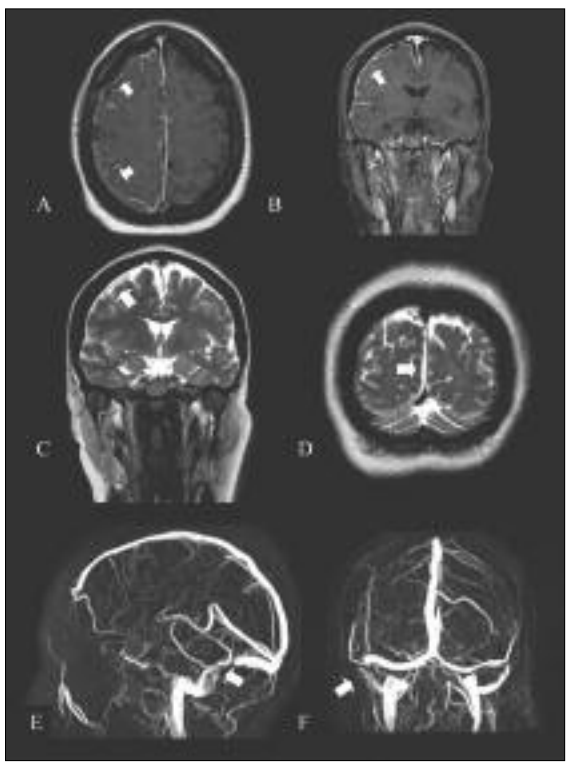

Figure 2 - The cerebral MRI with contrast show pachymeningitis of the right cerebral hemisphere (A, B) with a small subdural empyema (C, D). The angio-MRI shows a partial thrombosis of the right transverse sinus (E, F).

h), ampicillin (2 g every four hours, 12 g/24 h) and dexamethasone (8 mg, twice per day) all administered intravenously. Despite these actions, the patient developed generalized tonic-clonic seizures during the following hours. Benzodiazepine, phenytoin and levetiracetam failed to abolish the seizure activity. An emergency MRI of the brain revealed acute pachymeningitis of the right cerebral hemisphere (Figure 2, A-B) with a small subdural empyema

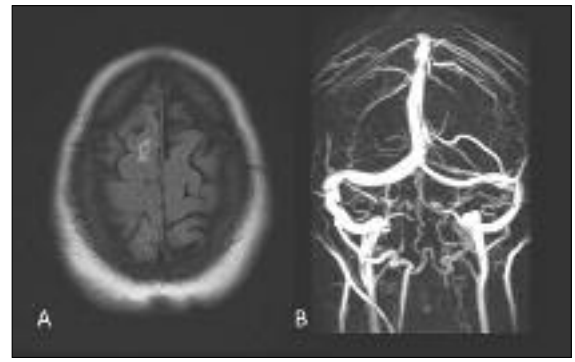

Figure 3 - Brain MRI performed five months later showed residual frontal cerebrocortical malacia instead of the initial empyema (A) with complete normalization of the right transverse sinus (B).

(Figure 2, C-D) and a partial thrombosis of the right transverse sinus (Figure 2, E-F). Therefore, anticoagulation was initiated with enoxaparin (8000 UI every twelve hours). Regardless, the patient developed a refractory status epilepticus (SE) without regaining consciousness. For this reason, it was decided to perform general anesthesia. Continuous EEG showed a rapid resolution of SE with a dosage of 0.2 mg/kg/h (3.3 γ/kg/min) of both midazolam and propofol. The next day a lumbar puncture was performed, which revealed pleocytosis (white cells 558/μl, 78% granulocytes and 22% monocytes), a normal glycorrhachia (77 mg/dl) and increased protein level (129 mg/dl). Propofol and midazolam were stopped on the third and fifth day, respectively, from the admission to the ICU. The patient regained consciousness on the seventh day and was discharged from ICU on the tenth day. Repeated MRI and CT scans of the brain showed resolution of the pneumocephalus and the cerebral empyema. The initial axial and coronal temporal bone CT scan showed a possible dehiscense of the tegmen tympany bone. This however was excluded by a second temporal bone CT scan a few days later which did not reveal any apparent osseous breach. Subsequent otorhinolaryngological evaluation did not indicate the need for surgical intervention. Ampicillin and cefotaxime were continued for 14 days. The cerebrospinal fluid (CSF) Gram stain revealed no organisms and the CSF culture was negative. *S. pyogenes*, however, was isolated from all six blood cultures and from the right ear drainage culture. Finally, an MRI performed five months later showed a complete normalization of the right transverse sinus and a small residual frontal cerebrocorti-

cal malacia instead of the initial empyema (Figure 3). After three months of rehabilitation the patient was able to return to her work.

DISCUSSION

We described a case of an atypical meningitis complicated by pneumocephalus, caused by a typically non-gas forming pathogen which is usually associated with a poor prognosis [3]. This case illustrates many important clinical-microbiological points. Pneumocephalus is defined as the presence of air or gas within any intracranial compartment of the cranial cavity [4]. Intracranial air is frequently seen in head and facial trauma, in congenital defects, in tumors of the skull base, following neurosurgery, or after otorhinolaryngological procedures [4]. Rarely has the presence of intracranial air been observed in patients with otogenic meningitis and concomitant mastoiditis, or as the results of the presence of gas-producing anaerobic bacteria [4-6].

Although there have been a few case reports describing pneumocephalus as a complication of bacterial meningitis in general, to the best of our knowledge this is the first case report of pneumocephalus and pachimeningities complicated by a *S. pyogenes* otogenic meningitis in an immunocompetent adult patient [5, 6]. *S. pyogenes* frequently colonizes the oropharynx but it usually does not invade the central nervous system directly [2]. It accounts for 0.2%-1% of all cases of adults meningitis with an annual incidence of 0.03 cases per 100,000 population [1, 3]. Only the report of Laupland et al. describes a *S. pyogenes* mastoiditis complicated by pneumocephalus in a previously healthy adult, yet without evidence of meningitis or cerebral abscess [7]. Two hypothetical mechanisms could explain the presence of air in the cranial cavity of our patient. The first is the invasion of mastoid air cells due to the possible bone destruction and forceful entry of air through a cranial defect with a sort of ball valve mechanism, especially during positive pressure events such as coughing or sneezing [4]. The second is the direct production of gas by the germs [4]. *S. pyogenes* is a Gram positive facultative anaerobic bacterium, which rarely produces gas in tissue by means of putrefaction of the intracellular protein or decomposition of glucose [8, 9]. In our patient, this last explanation is supported by the presence of air in the subdural space near the empyema (Figure 1 B and C, and Figure 2 B and C), by the integrity of the temporal bone on the subsequent CT scan, and finally by the resolution of the pneumocephalus after a few days of antibiotic therapy. Additionally, it is possible that the bacteria may have spread from the mastoid to the transverse sinus through venous drainage of the mastoid emissary vein, thus causing the partial thrombosis of the transverse sinus.

Although *S. pyogenes* infection is characterized by a high mechanism of virulence, it is still sensitive to most antibiotics. Therefore, prompt diagnosis and adequate antibiotic therapy could improve the prognosis [1-3]. Penicillin is the first-choice antibiotic for treatment of *S. pyogenes* meningitis [2]. Lumbar puncture (LP) and CT scan of the brain are the gold standards of diagnosis of cerebral infections, but they could have some limitations, especially to identify small intracranial abscesses [10]. LP should always be done when suspecting a CNS infection, after excluding intracranial hypertension. Here, however, the first brain CT scan showed cerebral edema and the subsequent general seizures had postponed the lumbar puncture. Consequently, empiric antibiotic therapy had been started. Although bacteremia without a focus is found in 15% of cases of invasive GAS infection, and in 59% of GAS meningitis, the interval between the start of antibiotic therapy and lumbar puncture in this patient could explain the absence of growing organism in the cerebrospinal fluid culture [11, 12].

The fulminant course of the infection in our patient is the result of the large number of virulence mechanisms involved in the complex pathogenicity of *S. pyogenes* [1, 2, 9]. Seizures occur in 32% of patients with *S. pyogenes* meningitis and in more than 52% of patients with bacterial empyema [3, 13]. Tonic-clonic status epilepticus is a medical emergency and treatment is aimed to stop the seizure in order to avoid cerebral damage. A patient with seizures that continue despite treatment with benzodiazepines and intravenous anti-epileptic drugs is said to have refractory status epilepticus. General anesthesia is usually recommended for refractory status epilepticus at a dose that results in EEG burst suppression [14]. The accurate diagnosis of the cerebrovascular complication due to bacterial infection revealed by the MRI study was essential for the right therapeutic treatment of this patient. Even though it was possible to manage the small empyema and the partial si-

nus thrombosis revealed by the MRI studies in this patient conservatively with antibiotics and anticoagulation, patients with these complications are in need of continuous neurological monitoring as to be able to perform immediate surgery in case of worsening of the neurological condition.

CONCLUSION

S. pyogenes meningitis, although rare, is a fulminant disease with high mortality and several neurologic sequelae, including pneumocephalus. Physicians should be aware that a prompt diagnosis and adequate antibiotic therapy may improve the prognosis, and that emergency MRI can easily show the neurovascular complications of a bacterial meningitis.

Conflict of interest
The authors have no funding or conflicts of interest to disclose.

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Keywords: *Streptococcus pyogenes*, pneumocephalus, meningitis, cerebral empyema, sinus thrombosis.

SUMMARY

Streptococcus pyogenes is a rare but aggressive cause of meningitis, which often evolves in a poor outcome with fatal consequences. Although lumbar puncture and CT scan of the brain are the gold standard of diagnosis of cerebral infections, they can have some limitations. We report and describe the clinical history and neuroimaging of a 36-year-old woman admitted to the emergency department of our hospital three days after the onset of earache and otorrhoea. When the patient developed an emergent refractory status epilepticus, the CT scan of the brain showed an unusual pneumocephalus. However, the MRI study of the brain revealed a pachymeningitis with partial thrombosis of the right transverse sinus and subdural empyema due to a *S. pyogenes* otitis media. Prompt diagnosis and the specific findings of the MRI allowed rapid correct treatment and thus led to a good outcome for the patient.

RIASSUNTO

Le meningiti causate dallo Streptococcus pyogenes *sono eventi rari e ciò nonostante caratterizzati da notevole aggressività e conseguenti elevate morbilità e mortalità. La puntura lombare e la TC dell'encefalo sono il* gold-standard *nella diagnosi di infezione cerebrale, tuttavia possono avere dei limiti. Riportiamo la storia e la descrizione del* neuroimaging *di una giovane trentaseienne presentatasi al nostro pronto soccorso a seguito di otalgia e otorrea. La TC encefalo eseguita a fronte dell'insorgenza di uno stato di male epilettico mostrava un inusuale pneumoencefalo. Tuttavia lo studio in emergenza in risonanza ha permesso di individuare una pachimeningite con iniziale empiema cerebrale e trombosi del seno trasverso rivelatasi dovuta ad una otite media complicata da* S. pyogenes. *La diagnosi precoce e le informazioni ottenute grazie alla MRI hanno permesso un rapido e preciso trattamento che ha consentito un buon esito per la paziente.*

REFERENCES

[1] Lamagni T.L., Darenberg J., Luca-Harari B., et al. Strep-EURO Study Group, Epidemiology of severe Streptococcus pyogenes disease in Europe. *J. Clin. Microbiol.* 46, 2359-2367, 2008.
[2] Crotti D., D'Annibale M.L., Ubaldi M., Fonzo G., Medori M.C. Pharyngotonsillitis caused by Streptococcus pyogenes: clinical and epidemiological aspects and resistance phenotypes towards macrolides. *Infez. Med.* 10, 213-219, 2002.
[3] Van de Beek D., de Gans J., Spanjaard L., Sela S., Vermeulen M., Dankert J. Group A Streptococcal meningitis in adults: Report of 41 cases and a review of literature. *Clin. Infect. Dis.* 34, e32-e36, 2002.
[4] Schirmer C.M., Heilman C.B., Bhardwaj A. Pneumocephalus: case illustrations and review. *Neurocrit. Care* 13, 152-158, 2010.

[5] Damergis J.A., Chee K., Amitai A. Otogenic pneumococcal meningitis with pneumocephalus. *J. Emerg. Med.* 39, e109-e112, 2010.
[6] Alviedo J.N., Sood B.G., Aranda J.V., Becker C. Diffuse pneumocephalus in neonatal Citrobacter meningitis. *Pediatrics* 118, e1576-e1579, 2006.
[7] Laupland K.B., Bosch J.D. Acute group A streptococcal mastoiditis complicated by pneumocephaly in a previously healthy adult. Scand. *J. Infect. Dis.* 38, 719-721, 2006.
[8] Cunningham M.W. Pathogenesis of group A streptococcal infections. *Clin. Microbiol. Rev.* 13, 470-511, 2000.
[9] Bisno A.L., Stevens D.L. Streptococcal infections of skin and soft tissues. *N. Engl. J. Med.* 334, 240-245, 1996.
[10] Viola S., Montoya G., Arnold J. Streptococcus pyogenes subdural empyema not detected by computed tomography. *Int. J. Infect. Dis.* 13, e15-e17, 2009.
[11] Sheehan J.P., Jane J.A., Ray D.K., Goodkin H.P. Brain abscess in children. *Neurosurg. Focus* 24, E6, 430-434, 2008.
[12] Shetty A.K., Frankel L.R., Maldonado Y., Falco D.A., Lewis D.B. Group A streptococcal meningitis: report of a case and review of literature since 1976. *Pediatr. Emerg. Care* 17, 430-434, 2001.
[13] Jim K.K., Brouwer M.C., van der Ende A., van de Beek D. Subdural empyema in bacterial meningitis. *Neurology* 79, 2133-2139, 2012.
[14] Shorvon S., Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 134, 2802-2818, 2011.