



Pneumocephalus as a rare complication: a systematic review plus clinical vignette

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ABSTRACT

Introduction. Pneumocephalus is a clinical entity characterised by the presence of gas in the intracranial space. It can result from many different causes. The most common cause is head or facial trauma. Other causes include neoplasms, infections, and surgical or diagnostic procedures. Spontaneous non-traumatic pneumocephalus is a rare condition caused by bone defects, malformations, infections, tumours, intravenous air injection, and other causes. This review, supplemented with a case presentation, aims to summarise the current state of knowledge regarding non-traumatic pneumocephalus.

Methodology. This review involved an electronic search (PubMed, Scopus, Embase, and Web of Science) to identify studies regarding non-traumatic pneumocephalus. In addition, reference lists of identified articles were screened for other potentially relevant papers.

Results. In total, 1,107 articles were retrieved by searching databases with the selected query. Based on the selection process, 134 articles were included. These articles were then classified into 'otogenic', 'bone defect', 'malformations', 'infectious', 'tumours', 'associated with intravenous air injection', and other categories.

Conclusion. Spontaneous non-traumatic pneumocephalus is a rare condition. Symptoms, clinical courses, and prognoses vary depending on the underlying cause of the disease. To the best of our knowledge, this review's example is the first case report of spontaneous pneumocephalus due to air embolism secondary to lung cancer.

Key words: pneumocephalus, spontaneous, non-traumatic, atraumatic

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Introduction

Pneumocephalus is characterised by the pathological collection of gas within the cranial cavity [1]. Pneumocephalus was first described in 1741 by Lecat et al. [2]. The main cause of pneumocephalus is head trauma, which is responsible for up to 74% of all

cases. Other causes of pneumocephalus include: (1) intracranial neoplasms; (2) infections; (3) neurosurgery; (4) paranasal sinus surgery; and (5) diagnostic or neurosurgical interventions such as pneumoencephalography or lumbar puncture [3].

However, in rare cases, pneumocephalus can occur spontaneously. Spontaneous occurrence represents only 0.6% of all

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cases and was first described in 1954 by Jelsma and Moore [4]. Based on anatomical localisation, pneumocephalus is classified as 'extradural', 'subdural', 'subarachnoidal', 'intraparenchymal' or 'intraventricular'. Two factors contribute to the pathomechanism of pneumocephalus: a decrease in intracranial pressure and coexisting defects in the dura. These factors are caused either by a ball-valve mechanism which causes a rapid increase in the volume of air inside the skull cavity without compensatory cerebrospinal fluid (CSF) outflow, or by CSF leakage which creates intracranial hypotension resulting in an aspiration of air [3, 5, 6].

Spontaneous non-traumatic pneumocephalus is a rare condition. Few case studies have been published to date [5]. The most common causes include (1) otogenic pneumocephalus, (2) bone defects, (3) malformations (birth defects), (4) infections, (5) tumours, (6) other causes, and (7) an intravenous injection of air. Here, we present the case of a patient with non-traumatic pneumocephalus, and provide a literature review on other non-traumatic cases.

Clinical vignette

Patient 1

A 66-year-old right-handed man with a past medical history of lung cancer was found at home, unconscious. His family reported a persistent hiccup, which had occurred the day before admission. Upon neurological examination, the patient was unconscious. He was intubated due to respiratory insufficiency, and his pupils were small, with anisocoria R > L and a poor response to light. He did not respond to pain stimuli. Computer tomography (CT) of the patient's brain showed a massive cerebral air embolism, which was later classified as an example of intra-axial intravascular pneumocephalus (Fig. 1). A thoracic CT scan revealed fluid and solid components of the left hilus with an obstruction of the left main bronchi (Fig. 2). After contrast enhancement, clear infiltration was observed, including the left pulmonary veins, left atrium, and left ventricle. An intra-infiltrating mass included lucencies, indicating the presence of gas or air. Left cardiac lung cancer infiltration with airway communication was strongly suspected. The patient died a few hours after his admission to the emergency department.

Methodology

The references used in the current review were primarily identified by performing a systematic search of the PubMed and Web of Science databases. The search queries used included 'pneumocephalus', 'spontaneous', 'non-traumatic', 'atraumatic', and 'cancer'. The title/abstract filter was used to broaden the search. The final search was performed in April 2020. In addition, reference lists of identified articles were screened for other potentially relevant papers. Articles were selected based on eligibility criteria. Studies were included if

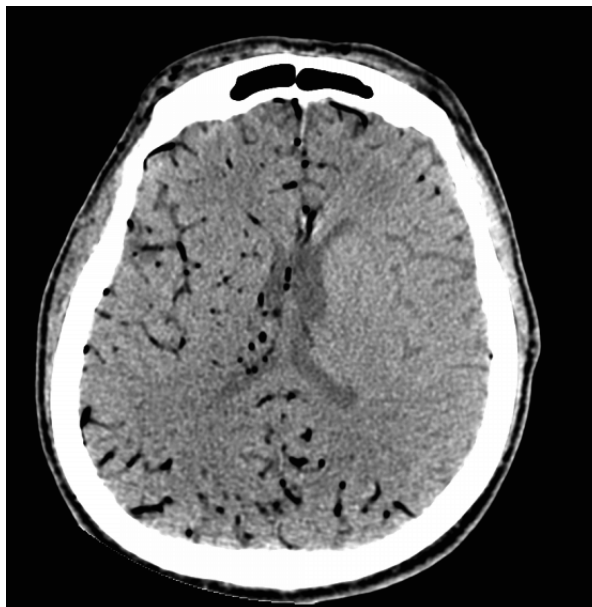


Figure 1. Brain CT. On axial CT, scan shows brain vessels with low density that indicates intravascular pneumocephalus



Figure 2. Chest CT. Axial CT-scan. Arrow indicates neoplasmic lung cancer and pulmonary vein infiltration with cancer mass, resulting in bronchial-vein fistula

(1) they presented original research, (2) they were conducted on pneumocephalus, and (3) they were written in English.

Selection process

In total, 1,107 articles were retrieved from the database search using the chosen queries (Fig. 3). Based on the selection process, 134 articles were included. These articles were then categorised as follows: (1) 'otogenic' (44 studies), (2) 'bone defect' (10 studies), (3) 'malformations' (five studies), (4) 'infectious' (38 studies), (5) tumours (30 studies), (6) others (four studies), and (7) associated with intravenous air injection (three studies).

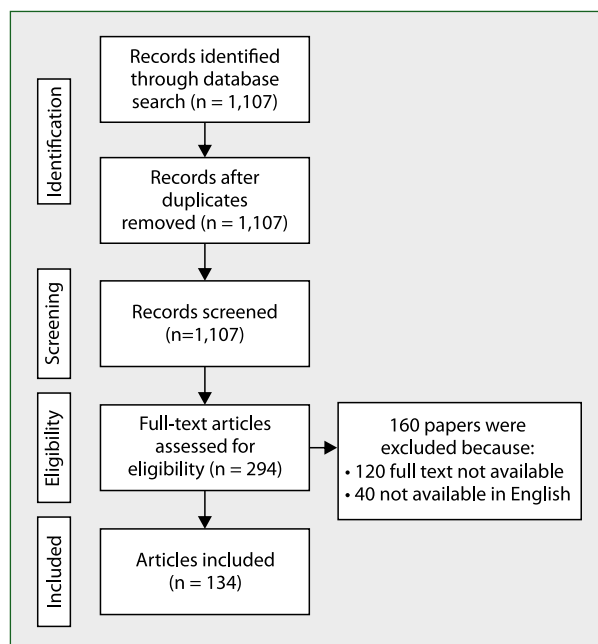


Figure 3. Selection process

Results

Spontaneous otogenic pneumocephalus (SOP)

A total of 44 articles were retrieved from the databases (Table 1). These articles were case studies reporting interesting patients and mechanisms of spontaneous otogenic pneumocephalus (SOP). The most common cause of SOP is a congenital bone defect in the pneumatized cells surrounding the middle ear. This defect develops into a fistulous communication with the intracranial compartment. Various factors can contribute to this mechanism, including: the Valsalva manoeuvre (coughing, sneezing, nose blowing, exhaling), the Politzer manoeuvre (blowing air through the nose during swallowing), and exposure to significant pressure changes (e.g. air travel) [7–11]. However, in a significant number of cases, the trigger remains unknown [12]. Wilkinson et al. reported a patient with intraventricular SOP related to barotrauma, which was due to tegmen defects that were confirmed in neuroimaging studies [13]. As such, bone defects in the middle cranial fossa have been proven to be associated with a risk of SOP occurrence [13]. Additionally, in SOP, hyperpneumatization of mastoids is a relatively common phenomenon [14]. Dowd et al. claimed that both a defect in the bones surrounding the middle ear (e.g. tegmen tympani defect) and a pressure difference on both sides of the defect are necessary for the formation of otogenic pneumocephalus [12]. Other descriptions of SOP in the literature support this theory [9,10,15]. Headache is the most common symptom of SOP, followed by aphasia [12, 16]. Villa et al. and Krayenbühl et al. reported a similar case of intraparenchymal pneumocephalus which manifested clinically with abnormal acoustic sensations, aphasia, and visual-field disturbances

[16,17]. The symptoms often described in the literature also include tinnitus, fullness in the ear, rhinorrhoea, nausea, and confusion [11,13,18,19].

Pneumocephalus associated with bone defects

A total of 10 articles were retrieved from the databases (Table 1). These articles contained case reports of pneumocephalus resulting from bone defects other than those related to SOP. In this group, the most frequent were defects of sphenoid sinus and cribriform plate causing hyperpneumatization of the cranium [20,21]. This process leads to communication between the inside of the skull and the intracranial compartment, which allows air to penetrate the cranium. Symptoms may be preceded by the Valsalva manoeuvre (e.g. blowing the nose, sneezing) [22, 23], though in a significant number of cases the triggers remain unknown [24]. Similarly to SOP, headache is the most commonly described symptom, along with rhinorrhoea [20, 24]. Nash et al. presented the case of a 27-year-old woman diagnosed with intraparenchymal pneumocephalus which manifested with a sudden onset of alien limb syndrome [9]. This rare phenomenon is most commonly described in cortico-basal syndrome and associated with frontal lobe and corpus callosum changes. For the reported patient, alien limb syndrome was related to pneumocephalus localised in the right frontal lobe, due to a cribriform plate defect. After treatment (pneumocephalus aspiration and bone defect repair), the patient recovered completely. Tension pneumocephalus is a relatively rare condition: only two articles contain case reports of tension pneumocephalus associated with bone defects [20, 25].

Pneumocephalus associated with malformations

A thorough search of the selected databases yielded a total of five articles on pneumocephalus associated with malformations. In all of these cases, pneumocephalus was associated with malformations related to an open myelomeningocele with accompanying CSF leakage [26]. In three of the five cases, pneumocephalus was localised intraventricularly [26–28]. The other locations were the posterior fossa and infratentorial area [29,30]. Spontaneous pneumocephalus occurs in a mechanism called the ‘reverse bottle effect’, which is attributed to CSF leakage through the neural tube defect. The air passes into the subarachnoid space and then through the spinal canal into the cranial cavity. In the case of open myelomeningocele, the air enters the spinal canal (e.g. when a child cries), which is associated with an increase of intracranial pressure accompanied by an outflow of CSF, leading to the formation of negative pressure in the ventricular system and an aspiration of air from outside [26,28]. The most commonly described symptoms are breathing difficulties and paresis of the lower limbs [27, 28].

Pneumocephalus associated with infections

A total of 37 articles on infections and pneumocephalus were retrieved from the databases (Table 1). Infections are a relatively common cause of pneumocephalus, and they

Table 1. Non-traumatic pneumocephalus: studies included in review

Authors [year]	Aetiology	Spontaneous otogenic pneumocephalus			
		Location	Symptoms	Location of air entry	Other
Barry [2019] [57]	Spontaneous	Posterior cranial fossa	Confusion, lethargy, myalgia, cough, fever	Mastoid	Mastoiditis, sinusitis, S. pneumoniae
Eggerstedt [2019] [58]	Spontaneous	Left temporal	Confusion, aphasia, otalgia, aural fullness	Mastoid	
	Spontaneous	Intraventricular, right middle cranial fossa	Altered mental status	Tegmen tympani	
	Spontaneous	Intraventricular	Headache, nausea, photophobia	Tegmen tympani, mastoid	
Harth [2019] [59]	Spontaneous	Left frontoparietal	Otalgia, hearing loss, tinnitus	Tegmen tympani	
	Spontaneous	Intraventricular	Balance problems, tinnitus, aural fullness, rhinorrhoea, weakness of right lower limb	Petrous bone	CSF leak
Pollaers [2019] [60]	Barotrauma (air travel)	Extradural	Headache, tinnitus, hearing loss, nasal obstruction, rhinorrhoea, postnasal drip	Mastoid	CSF leak
Voldřich [2019] [10]	Politzer manoeuvre	Middle cranial fossa	Vertigo, tinnitus, instability, aphasia	Tegmen tympani	Bilateral spontaneous pneumocephalus
Stewart [2018] [15]	Barotrauma (air travel)	Right middle cranial fossa	Vertigo, nausea, vomiting, headache, otalgia	Tegmen tympani, petrous	
Wu [2018] [61]	Valsalva manoeuvre (sneezing)	Left occipital lobe	Headache, dizziness, epistaxis, tinnitus, otorrhoea	Mastoid	CSF leak; subdural haemorrhage, maxillary hemosinus
Young [2018] [62]	Spontaneous	Intraventricular, right temporal lobe	Headache, rhinorrhoea, acute lethargy	Temporal bone	CSF leak
Arai [2017] [63]	Spontaneous	Intraventricular	Incontinence, dysarthria, imbalance, ear fullness	Petrous bone	Bilateral pneumocephalus
Guleria [2017] [64]	Spontaneous	Subarachnoid	Headache, vomiting, neck rigidity, otorrhoea	Chronic otitis media	
Wannemuehler [2016] [65]	Spontaneous	Frontal lobes	Anosmia, headaches, confusion	Tegmen tympani	'Mount Fuji sign'
Odani [2015] [66]	Spontaneous	Intracranial	Dizziness, fever	Gas forming bacteria	Streptococcus pneumoniae
Ratre [2015] [67]	Spontaneous	Left cerebellopontine angle	Fever, headache, vomiting, decreased hearing, neck rigidity	Chronic otitis media	
Ginat [2014] [68]	Barotrauma (air travel)	Intracranial	Dizziness, hearing loss	Dehiscent right superior semi-circular canal	
Pishbin [2014] [69]	Valsalva manoeuvre (coughing)	Intracranial	Headache, nausea	Pneumosinus dilatans	
Remenschneider [2014] [70]	Barotrauma (air travel)	Extradural	Vertigo, hearing loss,	Superior canal dehiscence	
Rabello [2013] [71]	Valsalva manoeuvre	Extradural parietal	Aural fullness, nasal obstruction, nasal pruritus, headaches	Mastoid	
Tamura [2012] [72]	Spontaneous	Intraventricular	Otalgia, otorrhoea, headache	Superior external auditory canal, mastoid	Brain abscess
Javan [2011] [73]	Barotrauma (air travel)	Cisternal	Confusion, fever, nausea, vomiting, weakness, headache	Bony defect	Air-fluid level in right sphenoid sinus



Table 1 cont. Non-traumatic pneumocephalus: studies included in review

Authors [year]	Aetiology	Spontaneous otogenic pneumocephalus			
		Location	Symptoms	Location of air entry	Other
Mohammed [2011] [74]	Valsalva manoeuvre (sneezing, nose blowing)	Extradural	Headache	Temporal bone	Subcutaneous emphysema
Zhao [2011] [75]	Spontaneous	Epidural	Mass in left occipital region, bilateral hearing deficits	Tegmen tympani	Tension pneumocephalus, occipital subcutaneous emphysema
Lee [2010] [76]	Spontaneous	Multifocal	Headache, nausea	Pneumosinus dilatans	
Murugesan [2010] [77]	Barotrauma (scuba diving)	Extradural	Headache, nausea, vomiting	Ethmoid	
Abbati [2009] [78]	Spontaneous	Left temporal lobe	Otalgia, aphasia, headache	Tegmen tympani, temporal bone	
Pennings [2009] [79]	Spontaneous	Extradural	ND	Mastoid	
Roberts [2009] [18]	Spontaneous	Intraventricular	Confusion, rhinorrhoea, urinary incontinence	Fistula - right sphenoidal recess, subsequently localised to right sphenoid sinus	CSF leak
Singh [2009] [9]	Valsalva manoeuvre	Left middle cranial fossa	Confusion	Tegmen tympani, temporal bone	
Hyam [2008] [80]	Spontaneous	Right middle cranial fossa, intraventricular	Confusion, aphasia	Mastoid, tegmen tympani	
Mathai [2008] [81]	Spontaneous	Intracranial	Fever, headache, vomiting, hearing loss	Chronic otitis media; 'gas forming' bacteria	
Tucker [2008] [19]	Valsalva manoeuvre (nose blowing)	Epidural	Headache, nausea	Mastoid	
Villa [2008] [17]	Spontaneous	Parenchymal (left temporal lobe)	Abnormal acoustic sensation, aphasia, visual field disturbances	Mastoid	
Bhattacharyya [2007] [82]	Spontaneous	Intracranial	Headache	Pneumosinus dilatans of frontal sinus	
Ciorba [2007] [83]	Spontaneous	Intracranial	Otalgia, headache, fever, otorrhoea, lethargy, nuchal rigidity, aphasia	Acute otitis media	Meningitis
Wilkinson [2007] [13]	Barotrauma (air travel)	Intraventricular	Tinnitus, hearing loss, aural fullness	Tegmen tympani	Temporal lobe fluid collection
Hage [2005] [11]	Change in altitude	Intraparenchymal, subdural, intraventricular	Abnormal acoustic sensations, deterioration, headache	Temporal bone	
Krayenbühl [2005] [16]	Spontaneous	Left temporal lobe	Abnormal acoustic sensations, aphasia, visual field disturbances	Mastoid	With intracerebral haemorrhage
Jensen [2004] [84]	Barotrauma (air travel)	Intraventricular	Headache, tinnitus	Mastoid	
Richards [2004] [8]	Valsalva manoeuvre (nose blowing)	Extradural	Swelling in ear area, otalgia	Mastoid	With collection of subcutaneous air
	Valsalva manoeuvre (coughing, sneezing, nose blowing)	Extradural	Pain and paraesthesia over left cheek and lower jaw	Mastoid	

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Table 1 cont. Non-traumatic pneumocephalus: studies included in review

Spontaneous otogenic pneumocephalus					
Authors [year]	Aetiology	Location	Symptoms	Location of air entry	Other
Schrijver [2003] [85]	Valsalva manoeuvre	Epidural	Asymptomatic	Mastoid	
Añorbe [2000] [86]	Valsalva manoeuvre	Right parietooccipital	Retroauricular swelling	Mastoid, petrous	With pneumatocele
Babl [1999] [87]	Valsalva manoeuvre	Subarachnoid	Headache	Sphenoid sinus	
Vallejo [1999] [14]	Valsalva manoeuvre	Right temporo-occipital	Headache	Mastoid	
Dowd [1998] [12]	Spontaneous	Intraventricular, left temporal cyst	Headaches, confusion, forgetfulness, aphasia, hemiparesis	Tegmen tympani	Abnormally low ICP
Maier [1996] [7]	Valsalva manoeuvre	Right parieto-temporo-occipital region, epidural	Headache, visual scotoma	Mastoid	
Pneumocephalus associated with bone defects					
Boninsegna [2019] [88]	Valsalva manoeuvre (nose blowing)	Subdural, intraventricular	Headaches	Cribriform plate	
Baba [2016] [23]	Valsalva manoeuvre (sneezing)	Extraaxial air (right cerebral hemisphere)	Headache, rhinorrhoea	Sphenoid sinus	CSF leak, CSF collection
Mirone [2015] [22]	Valsalva manoeuvre (nose blowing)	Intraparenchymal (left frontal lobe)	Loss of consciousness, hemiparesis, anosmia	Ethmoid sinus	
Gaberel [2012] [89]	Spontaneous	Intraventricular, intraparenchymal	Confusion	Sphenoid sinus	Arachnoid cyst
Nash [2012] [90]	Spontaneous	Intraparenchymal (right frontal lobe)	Alien limb syndrome	Cribriform plate	
Lefranc [2009] [20]	Spontaneous	Subarachnoid, intraventricular	Rhinorrhoea, headaches, epistaxis, anosmia	Cribriform plate	CSF leak; tension pneumocephalus
Tedeschi [2007] [21]	Spontaneous	Intraventricular, intraparenchymal	Headache, vomiting, fever, rhinorrhoea, nuchal rigidity, nystagmus	Sphenoid sinus	CSF leak
Kuo [2005] [25]	Spontaneous	Subarachnoid	Headache, rhinorrhoea, neck rigidity	Sphenoid sinus	Tension pneumocephalus, CSF leakage
Hogg [1998] [91]	Spontaneous	Intracranial	Rhinorrhoea, left hemiparesis, headache	Sphenoid sinus	
Park [1998] [24]	Spontaneous	Epidural	Headaches	Bone defect	Hyperpneumatisation of cranium
Pneumocephalus associated with malformations					
Kutty [2018] [28]	Spontaneous	Intraventricular	Apnoea, muscular hypotonia in lower limbs and sphincter	Open myelomeningocele	CSF leak
Erol [2004] [29]	Spontaneous	Infratentorial area	Apnoea attacks	Open lumbosacral myelomeningocele	CSF leak
Oedemis [2004] [27]	Spontaneous	Intraventricular	Lower limb paralysis	Open lumbosacral myelomeningocele	CSF leak; with infection
Garonzik [2001] [30]	Spontaneous	Posterior fossa	Open lumbosacral myelomeningocele	CSF leak	
Trawöger [1994] [26]	Spontaneous	Intraventricular	Respiratory distress	Open lumbosacral myelomeningocele	CSF leak; with infection

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Table 1 cont. Non-traumatic pneumocephalus: studies included in review

Authors [year]	Aetiology	Pneumocephalus associated with infections			
		Location	Symptoms	Location of air entry	Other
Mirzai [2019] [92]	Spontaneous	Intracranial	Abdominal pain, weakness, confusion, constipation	Gas-forming Clostridium septicum	DM type 1
Saleem [2019] [93]	Spontaneous	Intracranial	Confusion, disorientation, fever, headache, vomiting	Bacterial infection	Sinusitis, pansinusitis, subdural empyema
Sun [2019] [94]	Spontaneous	Intracranial	Headache, nasal congestion, vertigo	Gas-forming Haemophilus influenzae	Mucopyocele
	Spontaneous	Intracranial	Fever, frontal headaches, cough, rhinorrhoea	Gas-forming Staphylococcus aureus and Escherichia coli	Meningitis
Ansari [2018] [95]	Spontaneous	Intracranial	Headache, lethargy, deterioration	Gas-forming Streptococcus salivarius	CPAP use complication, sinus wall osteomyelitis
Kumari [2017] [96]	Spontaneous	Subdural and subgaleal	Refusal to feed, progressive increase in head size, hypothermic	Possible bacterial infection	Neonatal meningitis, 'air bubble sign'
Srikumar [2017] [97]	Spontaneous	Intracranial	Left arm clumsiness, altered mental status, fever	Aspergillus terreus	Angiosarcoma
Lin [2014] [98]	Spontaneous	Intracranial	Fever, confusion, anisocoria	Bacterial meningitis with gas-forming organisms	Air embolism
Subasree [2014] [99]	Spontaneous	Intracranial	Headache, fever, neck rigidity	Gas-forming Bacteroides fragilis	
Kim [2013] [31]	Spontaneous	Intraventricular	Night sweats, confusion, headache	Streptococcus pneumoniae	Meningitis
Kosac [2013] [100]	Spontaneous	Intracranial	Headache, vomiting, persistent aqueous rhinorrhoea	Opacification of left sphenoid sinus and bone defect of left pterygoid process	Chronic sinusitis
Rota [2013] [101]	Spontaneous	Intracranial	Comatose state, fever	Gas-forming Streptococcus pneumoniae	Pneumococcal meningitis, right mastoiditis and left ethmoid sinusitis
Shenoi [2013] [37]	Spontaneous	Subarachnoid, intraparenchymal, intravascular	Hypothermia, lethargy, feeding difficulty	Citrobacter koseri	Late-onset neonatal Citrobacter meningitis
Baig [2012] [32]	Spontaneous	Subarachnoid space	Headache, rhinorrhoea, vomiting, fever, meningeal signs, bilateral papilledema	Bony erosion around olfactory cleft	Nasal tuberculosis
Kaur [2012] [102]	Spontaneous	Subdural	Fever, headache, convulsions, neck rigidity, positive Kernig sign	Meningitis	
Bhogal [2011] [103]	Spontaneous	Intraparenchymal	Diarrhoea, vomiting, altered level of consciousness, generalised weakness	Gas-forming Clostridium septicum	Cerebritis
Kumari [2011] [104]	Spontaneous	Intraparenchymal, intraventricular	Abnormal behaviour, fever, headache, back and neck pain vomiting, coughing	Gas-forming Staphylococcus aureus	Staphylococcal pneumonia and meningitis
Martin [2011] [35]	Spontaneous	Intraparenchymal	Anuria, bloody diarrhoea	Clostridium septicum gas – producing bacteria	Haemolytic uremic syndrome

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Table 1 cont. Non-traumatic pneumocephalus: studies included in review

Authors [year]	Aetiology	Pneumocephalus associated with infections			
		Location	Symptoms	Location of air entry	Other
Oh [2011] [105]	Spontaneous	Intracranial	Fever, fatigue	Bony erosion, Tuberculosis meningoencephalitis	Lupus erythematosus
Redhu [2011] [33]	Spontaneous	Intracranial	Headache, dizziness, fever, unconscious with tonic extensor response to pain	Escherichia coli	Subdural empyema
Damergis [2010] [106]	Spontaneous	Intracranial	Headache, photophobia, nausea, jaw discomfort, subjective fever	Streptococcus pneumoniae	Otogenic meningitis
Lasboo [2010] [107]	Spontaneous	Subarachnoid	Altered mental status, urinary incontinence, diarrhoea, lower back pain	Gas-forming Escherichia coli	Septic discitis, meningitis, solid organ abscesses, urosepsis
Chung [2009] [108]	Spontaneous	Subarachnoid	Right hypertonia, hyperreflexia, confusion, dysphasia, right facial droop	Fistula between subarachnoid space crania extension of cervical spine	Nasopharyngeal carcinoma, osteoradionecrosis, osteomyelitis
Hama-Amin [2009] [109]	Spontaneous	Subarachnoid, intraparenchymal, intraventricular	Headache, confusion, somnolentia, meningeal signs	Gram-negative bacterial meningitis	
Lin [2009] [34]	Spontaneous	Intracranial	Headache, vomiting, fever, nasal congestion, neck stiffness, meningeal sign	Candida albicans sphenoid sinusitis	Pus drained from right sphenoid cavity
Kuo [2008] [38]	Spontaneous	Intracranial	Consciousness loss, hypothermia	E. cloacae	Nosocomial meningitis
Sreejith [2008] [110]	Spontaneous	Subarachnoid	Headache, fever, vomiting, ear discharge, hearing impairment, meningeal sign	Klebsiella pneumoniae meningitis	
Alviedo [2006] [39]	Spontaneous	Intracranial	Lethargy, apnoea, pallor, hypothermia	Citrobacter koseri	Meningitis
Townend [2005] [111]	Spontaneous	Intraventricular	Confusion, fever	Streptococcus pneumoniae	Sinusitis
Parmar [2004] [112]	Spontaneous	Intracranial	Lower back pain, fever, night sweats	Gas-forming Bacteroides fragilis	Meningitis
Pooboni [2004] [113]	Spontaneous	Intracranial	Poor feeding, state of collapse, hypothermia, hypotension	Gas-forming Citrobacter koseri	Pneumatosis oculi
Sedaghatian [2004] [114]	Spontaneous	Intracranial	Fever, irritability, convulsions	Gas-forming Enterobacter cloacae	Enterobacter cloacae septicemia and neonatal meningitis
Kassim [2003] [115]	Spontaneous	Intracranial	Poor feeding, lethargy, hypotensive, generalised convulsions	Gas-forming Proteus mirabilis	Meningitis
Goyal [1996] [116]	Spontaneous	Intracranial	Fever, hypotensive, altered sensorium	Gas-forming Clostridium perfringens	Meningitis
Randall [1993] [117]	Spontaneous	Intracranial	Bloody diarrhoea, abdominal pain, seizure, coma	Gas-forming Clostridium septicum	Retinal haemorrhages
Finelli [1991] [118]	Spontaneous	Intraventricular, subarachnoid	Focal left-sided seizure, eye deviation to left, confusion, hyperreflexia	Gas-forming Streptococcus pneumoniae	Meningitis
Candan [1990] [36]	Spontaneous	Intracranial	Otorrhoea, fever, nausea, vomiting, headache, epilepsy attack, left hemiparesis, neck stiffness	Gas-forming organisms: Proteus mirabilis, Veillonella spp.	Abscess in right temporal lobe



Table 1 cont. Non-traumatic pneumocephalus: studies included in review

Pneumocephalus associated with infections					
Authors [year]	Aetiology	Location	Symptoms	Location of air entry	Other
Holtby [1990] [119]	Spontaneous	Intracranial	Earache, headache, nausea, vomiting, confusion, neck rigidity	Gas-forming Streptococcus pneumoniae	
Klein [1989] [120]	Spontaneous	Intraparenchymal, intraventricular, subarachnoid	Irregular respiration, hypotension	Gas-forming Clostridium perfringens meningoencephalitis	
Pneumocephalus associated with tumour					
Ghimire [2019] [50]	Spontaneous	Intraventricular	Mutism, right hemiparesis, deterioration	Defect in sphenoid sinus	Echordoid physaliphora (EP)
Iplikcioglu [2019] [121]	Spontaneous	Intracranial	Headache, drowsiness, vomiting	Posterior wall of frontal sinus	Front ethmoid osteoma
Elabd [2018] [122]	Spontaneous	Intraventricular	Headache, nausea, rhinorrhoea	'One-way valve mechanism' spontaneous to cabergoline treatment	
Albert [2017] [123]	Spontaneous	Intracranial	Cough, haemoptysis, right chest and back pain, right arm weakness	Bronchopleural-dural fistula	Chemoradiation, superior sulcus tumour
Hackenbroch [2017] [124]	Spontaneous	Intraparenchymal, right frontal lobe	Headache, difficulty with concentration, left arm weakness	Erosion of posterior wall of frontal sinus	Sinonasal osteoma, 'one-way valve mechanism'
Umredkar [2017] [125]	Spontaneous	Intracranial	Headache, left side hemiparesis	Erosion of posterior wall of frontal sinus	Frontal sinus osteoma, 'ball valve mechanism'
Jimenez [2014] [126]	Spontaneous	Intraventricular	Aqueous rhinorrhoea, altered mental condition	Nasocranial fistula	Nasopharyngeal carcinoma, radiotherapy
Marchant [2013] [127]	Spontaneous	Intraventricular, air in thoracic spinal canal	Headache	Oesophageal-arachnoid fistula	Non-small cell lung carcinoma
Nanba [2013] [128]	Spontaneous	Intraventricular and subarachnoid spaces	Headache, vomiting, delirious. CSF rhinorrhoea	Cabergoline treatment	MEN-1, macroprolactinoma, treatment with cabergoline
Patel [2013] [49]	Spontaneous	Intraventricular	Headache	Oesophageal-subarachnoid fistula	Oesophageal cancer
Iacoangeli [2012] [48]	Spontaneous	Subdural (bifrontal), pneumorrhachis	Headache, confusion	Sacral bone	Colon adenocarcinoma
Lehmer [2012] [41]	Spontaneous	Intracranial	Headache, nausea, vomiting	Destruction of posterior wall of frontal sinus	Osteoma, one-way valve mechanism
Machicado [2012] [43]	Spontaneous	Subarachnoid, intraventricular	Rhinorrhoea, vomiting, headache	Cabergoline treatment	Macroprolactinoma
Guedes [2011] [129]	Spontaneous	Intraparenchymal	Headache, right hemiparesis, seventh cranial nerve palsy	Bone erosion	Fronthoethmoidal osteoma
Qu [2010] [45]	Spontaneous	Subdural (bifrontal), vertebral canal	Headache, altered consciousness	Subarachnoid-oesophagus fistula	Oesophageal cancer; 'Mount Fuji sign'
Chung [2009] [130]	Spontaneous	Intracranial, subarachnoid	Confusion, expressive dysphasia, right facial droop, right-sided hypertonia and hyperreflexia	Osteoradionecrosis of cervical spine	Nasopharyngeal cancer, meningitis
Kamide [2008] [40]	Spontaneous	Intraparenchymal	Headache, left hemiparesis	Erosion of upper wall of ethmoid sinus	Osteoma in ethmoid sinus

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Table 1 cont. Non-traumatic pneumocephalus: studies included in review

Authors [year]	Aetiology	Pneumocephalus associated with tumour			
		Location	Symptoms	Location of air entry	Other
Torres [2008] [131]	Spontaneous	Spinal canal	Tightness in thigh muscles, pain in perineal area	Gas communication between carcinoma of sigmoid colon into spinal canal	Carcinoma of sigmoid colon
Wang [2006] [44]	Spontaneous	Intraparenchymal, intraventricular	Headache, vomiting, blurred vision, rhinorrhoea, consciousness disturbances	Skull base defect; high-dose radiotherapy	Nasopharyngeal carcinoma
Bramley [2001] [132]	Spontaneous	Intracranial	Left hemiparesis	Erosion of right ethmoid sinus wall and right orbit	Ethmoid osteoma
Wu [1999] [133]	Spontaneous	Intraventricular, intracranial	Nasal discharge, loss of consciousness	Bony defect in right sphenoid body	Ventricular fluid revealed Staphylococcus infection
Jakubowski [1997] [134]	Spontaneous	Intracranial	Forgetfulness, left hemiparesis, anisocoric pupils	Bony destruction	Diploic epidermoid cyst
Kiu [1996] [135]	Spontaneous	Intraventricular, subarachnoid, subdural	Headache, rhinorrhoea, deterioration, neck stiffness	Destruction of skull base by tumour	Tension pneumocephalus; nasopharyngeal carcinoma, meningitis
Ng [1995] [136]	Spontaneous	Intracranial	Headache, fever, multiple nerve palsy	Noso-cranial fistula, bone necrosis	Nasopharyngeal carcinoma, radiotherapy
Kinsley [1993] [42]	Spontaneous	Intracranial	Left-side weakness, headache, confusion, drowsiness, decreased taste and smell	Bone defect in sinus	Epidermoid tumour of ethmoid sinus origin
Swaid [1983] [46]	Spontaneous	R frontal fossa	Headache, neck pain, confusion	Bronchial-subarachnoid fistula	Lung carcinoma
Lynn [1978] [51]	Spontaneous	Intracranial	Fever, irritability, poor feeding	Neurenteric fistula	Benign teratoma, meningitis
Banerjee [1975] [137]	Spontaneous	Intracranial	Headache, vomiting	Dural defect	Osteoid osteoma of ethmoid
Wilson [1968] [138]	Spontaneous	Intracranial	Brown-coloured discharge from left nostril	Destruction of frontal sinus wall	Epidermoid tumour
Holmes [1957] [47]	Spontaneous	Intraventricular	Nasal obstruction, exophthalmos, headache	Cribriform plate	Sarcoma of ethmoid
Pneumocephalus associated with intravenous air injection					
Laurent [2014] [53]	Spontaneous	Right cavernous sinus, right inferior ophthalmic vein, left cavernous sinus, right sphenoid sinus	Asymptomatic	Peripheral intravenous catheter	Ripped out intravenous catheter
Tran [2010] [52]	Spontaneous	Right cavernous sinus, right superficial temporal veins, left intraorbital veins	Asymptomatic	Peripheral intravenous catheter	
	Spontaneous	Right cavernous sinus, right superficial temporal veins, right superior orbital veins	Asymptomatic	Peripheral intravenous catheter	
	Spontaneous	Bilateral cavernous sinus, behind dorsum sella, right superficial temporal veins	Asymptomatic	Peripheral intravenous catheter	

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Table 1 cont. Non-traumatic pneumocephalus: studies included in review

Pneumocephalus associated with intravenous air injection					
Authors [year]	Aetiology	Location	Symptoms	Location of air entry	Other
Syed [2008] [54]	Spontaneous	Intracranial	Visual disturbances, headache, dizziness	Intravenous catheterisation	Gas emboli
Pneumocephalus associated with other aetiology					
Isikay [2018] [55]	Spontaneous	Subarachnoid	Generalised seizures	Interruption in cervical dural sheath	Positive end ventilation
Akashi [2015] [139]	Spontaneous	Intracranial	Headache, nasal hyrorrhoea	Nasal fistula	Granulomatosis with polyangiitis
Miyaji [2013] [140]	Spontaneous	Subarachnoid, intraventricular, pneumatocele in spinal canal	Headache, fever	Fistula in sacral region	Pressure ulcer
Park [2010] [56]	Spontaneous	Epidural	Headache	'One-way valve' mechanism	

represent 8.8% of all cases [3]. Bacterial infections are the most common, and they can cause subdural empyema with meningitis, leading to spontaneous pneumocephalus [31–33]. Two possible pathways were described: (1) an infection with 'gas-forming' bacteria and (2) a bony erosion caused by bacteria. Redhu et al. described a case of spontaneous tension pneumocephalus associated with subdural empyema caused typically by *Escherichia coli*. Pneumocephalus, therefore, resulted from an accumulation of gases in the nerve tissue as a result of bacterial metabolism [33]. Baig et al. presented a case of spontaneous pneumocephalus associated with nasal tuberculosis. As a result of a *Mycobacterium tuberculosis* infection, bone erosion around the olfactory cleft occurred, with subsequent dura mater damage and CSF leakage [32]. Lin et al. described a case of spontaneous pneumocephalus associated with sphenoid sinusitis caused by *Candida albicans*. Extensive fungal osteomyelitis caused bone erosion of the right sphenoid sinus and resulted in intracranial pneumocephalus [34]. Martin et al. presented a case of spontaneous pneumocephalus associated with haemolytic uremic syndrome. As a result of *Clostridium septicum*-induced sepsis, many pockets of pneumocephalus created a 'Swiss cheese' appearance on brain CT scans [35]. The symptoms are typical for meningitis: headache, fever, vomiting, and night sweats (Tab. 1) [31, 33, 36]. Tension pneumocephalus as a result of bacterial meningitis is usually fatal [37–39].

Pneumocephalus associated with tumours

A thorough search of the databases revealed a total of 30 articles of pneumocephalus associated with tumours (Tab. 1). Pneumocephalus related to tumours has mostly been associated with sinus osteomas, followed by epidermoids, pituitary tumours, and nasopharyngeal carcinomas [40–44]. Different factors can destroy the tissues surrounding tumour cells, such as fistulae between the posterior wall of the oesophagus and the subarachnoid space of the spinal cord, which contribute to trapping air in the cranial cavity or in subdural spaces [45]. Additionally, pneumocephalus can be

caused by radionecrosis as a result of treatment (e.g. subarachnoid bronchial fistulae as a result of irradiation therapy) [44, 46]. Furthermore, tension pneumocephalus can occur spontaneously as a result of treating dopaminergic agents with cabergoline [47, 48]. The main symptoms include headache, rhinorrhoea (presumably CSF), and confusion [45–49]. Interestingly, Torres et al. described a patient with stiffness in their thigh muscles and perineal areas as a result of gas collection in the subdural layer of the sacral nerve root [50]. Lynn et al. presented a case of spontaneous pneumocephalus with neurenteric communications in the form of a neurenteric fistula [51]. Wang et al. presented an interesting case of tension spontaneous pneumocephalus due to intensive high-dose radiotherapy, which caused osteoradionecrosis of the skull base and CSF leakage [44]. Interestingly, Kinsley et al. described a patient with tension pneumatocele originating from an epidermoid tumour. The patient developed symptoms for six months prior to his admission, which shows that the signs of pneumocephalus can develop either severely, within the first 24 hours of occurrence, or slowly progress over weeks or even months [42].

Pneumocephalus associated with an intravenous injection of air

The database search revealed only three articles on intravenous-related pneumocephalus (Tab. 1). This is considered a rare cause of pneumocephalus, usually related to the placement of an intravenous catheter [52]. Laurent et al. reported a patient with pneumocephalus resulting from an air embolism caused by a ripped-out peripheral intravenous access [53]. Tran et al. suggested that the diagnosis of intravenous-induced pneumocephalus should be considered in every case of incidentally detected air in the cranial cavity venous system on CT scans unless a medical reason is known [52]. In the reported cases, the most common location of pneumocephalus was the sinus cavernous [52, 53]. Intravenous-related pneumocephalus is associated with a good prognosis [54]. Pneumocephalus associated with an air embolism usually remains asymptomatic [52, 53].

Pneumocephalus associated with other aetiologies

Four case reports on the occurrence of spontaneous pneumocephalus related to other factors which could not be classified as belonging to the above-mentioned groups, were found in the chosen databases (Tab. 1). Isikay et al. reported an infant with bronchopneumonia who developed pneumocephalus as a result of positive ventilation during treatment for bronchopneumonia [55]. A generalised inflammatory reaction can disrupt the nerve sheaths, which – in combination with positive pressure ventilation – can result in air entering the subarachnoid spaces. Park et al. reported a case of pneumocephalus resulting from pneumatocele in the frontal sinus [56]. Air entered through the frontal sinus ostium but was unable to exit, which increased pressure in the sinus and caused subsequent expansion. The most common symptoms include headache and nausea, but also generalised seizures [55, 56].

Discussion

To the best of our knowledge, ours is the first case report of spontaneous pneumocephalus due to air embolism secondary to lung cancer. In our case, lung cancer caused infiltration of the left atrium and the left ventricle; therefore, air from the left ventricle entered the aorta and then travelled through the brachiocephalic trunk and carotid arteries into cerebral circulation, causing a massive air embolism.

Spontaneous intravenous pneumocephalus caused by an air embolism is a rare condition – so far, only three cases have been described [51–53]. An air embolism underlying pneumocephalus can affect both the arterial and venous vessels. In contrast to our case, the remaining reports presented pneumocephalus due to venous embolism as a result of intravenous air injection through a peripheral venous catheter [51, 52]. Patients with intravenous pneumocephalus can show acute symptoms within the first 24 hours of occurrence, similar to the patient presented here, or can show slowly progressing signs within weeks [47]. The course of the disease in the presented patient was acute, accompanied by disturbances of consciousness and respiratory failure resulting in death. In contrast, Laurent et al. describe a mild, asymptomatic course of pneumocephalus related to intravenous air injection through a peripheral venous catheter [51, 52]. However, Syed et al. reported that the patient experienced visual disturbances, headache, and dizziness due to gas embolism during intravenous catheterisation [53].

Our review of the literature confirms that the most common causes of pneumocephalus are otogenic and infectious, followed by tumours. A minority of pneumocephalus cases are caused by intravenous air injection and other cases.

Symptoms and the clinical course of pneumocephalus can vary, depending primarily on aetiology and the location of intracranial gas. The most frequent symptoms, regardless of pneumocephalus aetiology, are headaches and consciousness

disturbances [30, 59, 99, 120]. In otogenic spontaneous pneumocephalus, otalgia, aural fullness, hearing loss, tinnitus, otorrhoea, and abnormal acoustic sensations are also often described. In pneumocephalus caused by infections, fever and meningeal symptoms are the most common symptoms [31, 92, 98, 108].

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