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Spontaneously arising disease

Air leak syndrome in animals: definition and pathogenesis

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ABSTRACT

Air leak syndrome (ALS) is described in human medicine as a constellation of clinical disorders including pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema, pneumothorax, pneumoperitoneum, pneumoretroperitoneum and subcutaneous emphysema. The pathogenesis of ALS depends on the anatomy of the mediastinum and its associations with thoracic, abdominal and cervical connective tissues, as well as a physical phenomenon referred to as the Macklin effect. Various animal species develop diverse combinations of these lesions, although ALS has not been recognized in animals. However, this term aids pathologists in addressing this disease compilation. The aim of this retrospective study is to illustrate examples of ALS in animals by arbitrarily selecting 13 cases in dogs, cats, pinnipeds, sea otters and harbour porpoises. ALS can be classified into three groups based on aetiology: iatrogenic, secondary or spontaneous. Iatrogenic ALS was diagnosed in two cats with tracheal laceration following endotracheal intubation. Secondary ALS was identified in two dogs, one with acute respiratory distress syndrome and the other due to grass awn migration. Secondary ALS in pinnipeds was diagnosed following severe pulmonary parasitism, uraemic pneumonia and oesophageal perforation. The other marine mammals developed ALS following trauma. Spontaneous ALS was also diagnosed in one cat and one dog without any apparent predisposing causes.

1. Introduction

Air leakage is a clinical phenomenon that is associated with the escape of air from a cavity, which naturally contains air, into tissues or potential spaces that under normal circumstances must not contain air [1]. The concept of air leak syndrome (ALS) is well established in human medicine where the most commonly reported presentations are pneumomediastinum (PM), subcutaneous emphysema (SE), pneumoretroperitoneum (PRP) and pneumopericardium (PPC) followed by less commonly reported pneumothorax (PTX), pulmonary interstitial emphysema (PIE) and pneumoperitoneum (PP) [1–3]. Although in many cases these conditions occur alone, it is more common to find the leaked air in different anatomical compartments simultaneously, due to the dissipation of air from one space to other spaces, making it difficult or even impossible to detect the initial site of egress [1].

The pathogenesis of such lesions or combinations of lesions is generally associated with disruption of one or more anatomical structures:

- direct leakage from an airway or the oesophagus into the mediastinum;
- laceration or dissection of the pulmonary parenchyma resulting in leakage into the pulmonary interstitium. Air can then track between fascial sheaths and the adventitia of blood vessels and bronchi towards the hilus and eventually into the mediastinum (Macklin effect);
- perforation of a gas-containing abdominal viscus followed by air tracking along the adventitia of blood vessels into the thorax and mediastinum; or
- tracking of air from the fascia of the neck caudally into the mediastinum [4–5].

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ALS classification also relies on aetiology, which is determined by the origin of the air leakage, whether intrathoracic or extrathoracic [6]. If the origin is extrathoracic (neck, face, cervical oesophagus or larynx), air may dissect along fascial tissue planes into the mediastinum and subcutis. It may communicate with the fascial planes of the neck cranially through the thoracic inlet and also dissect caudally into the retroperitoneal space through the aortic hiatus [6,7]. Nonetheless, when the dispersed air originates within the intrathoracic region (including the distal trachea, bronchi, bronchioles and alveoli), the air reaches the mediastinum due to the Macklin effect. Essentially, this mechanism denotes that the sudden rise in intra-alveolar, bronchial or bronchiolar pressure results from rupture of the alveolar parenchyma, a bronchus or bronchioles. Subsequently, the expelled air dissects centripetally through the pulmonary interstitium along the bronchovascular sheaths towards the pulmonary hila to reach the mediastinum, which has somewhat negative pressure with respect to the pressure in the pulmonary parenchyma [4,6,8,9].

Different combinations of these lesions have been documented in various animal species but have been inadequately explored, lacking comprehensive insights into the underlying pathophysiology and associated factors. While van den Broek [7] provided an anatomical elucidation of the canine mediastinum, offering an explanation for cases involving PRP and SE as secondary to PM, with similarities to these conditions in humans, scant published studies have delved into these anatomical communication pathways or the Macklin effect in other animals [7].

To the authors' knowledge, the designation ALS has remained absent and lacks substantial recognition within the domain of veterinary pathology. Nevertheless, grasping the pathogenesis of this syndrome holds diagnostic significance, as it would facilitate integration of the different lesions and assist in identifying the causes or predisposing factors. Therefore, the aim of this work is to introduce the concept of ALS into veterinary pathology describing the concomitant presence of PM, PTX, PRP and SE in arbitrarily selected necropsy cases representing both domestic and free-ranging mammals. We also propose a classification of ALS cases based on established standardization in human pathology.

2. Materials and methods

2.1. Case selection, necropsy and tissue processing

In this retrospective study, cases were selected from the Servei de Diagnòstic de Patologia Veterinària database at the Universitat Autònoma de Barcelona and The Marine Mammal Center (TMMC) in Sausalito, California, USA. The cases included cats (n = 3), dogs (n = 3), California sea lions (*Zalophus californianus*) (n = 2), Pacific harbour seals (*Phoca vitulina richardii*) (n = 2), Southern Sea otters (*Enhydra lutris nereis*) (n = 2) and one odontocete cetacean, a harbour porpoise (*Phocoena phocoena*) (n = 1). Cases were selected on the basis of post-mortem findings by assessing the presence of trapped air in the various body compartments, with no evidence of thoracic wall perforation, and validated with pre-mortem diagnostic imaging. Additionally, case selection relied on clinical records of unexplained respiratory distress or euthanasia, with or without a history of previous surgery or traumatic injuries.

Case 1 was a 7-year-old male cat obtained from an animal body donation programme, with an undisclosed history (Table 1). Cases 2 and 3 were a 6-month-old and an 8-year-old female cat, respectively, and case 4 was a 6-year-old female dog. Notably, in these three instances, respiratory distress had developed several weeks after surgical procedures (ovariohysterectomy and coxofemoral dislocation) with endotracheal intubation. Case 5 was a 7-year-old male dog that had acute respiratory distress accompanied by sudden jaundice, diarrhoea and haematemesis. The pre-mortem haemogram revealed significant anaemia, mild neutrophilia and lymphocytosis. Biochemical serum analysis indicated elevated activities of liver enzymes (ALT, ALKP, GGT) and total bilirubin as well as azotaemia and uraemia. Diagnostic polymerase chain reaction and enzyme-linked immunosorbent assay testing on urine and plasma indicated an infection by *Leptospira* spp (details not provided). Case 6 was a 1.5-year-old female dog that had unexplained respiratory distress characterized by tachypnoea, persistent coughing and sneezing over a period of 1 week, ultimately leading to euthanasia due to the development of a severe tension PTX. In cases 2, 4 and 6 ante-mortem radiography revealed SE, PM, PRP and bilateral PTX (Supplementary Fig. S1). Case 7 was a weaned male harbour seal pup (approximately 4–5 months old) found in distress on a beach with extensive lacerations to the pelvic flippers and pelvis consistent with a recent shark bite. It died in transit to TMMC. An adult female harbour seal (case 8) was found emaciated and lethargic on a beach. On clinical examination, cervical and thoracic radiographs revealed a thoracic oesophageal mass and interstitial pulmonary emphysema. Euthanasia was elected because of the poor prognosis. A yearling female California sea lion (case 9) was found stranded in poor body condition and lethargic, and died shortly after rescue. Case 10 was a juvenile male California sea lion found stranded with lethargy, emaciation, azotaemia (markedly elevated BUN and creatinine) and hyperphosphataemia clinically suggestive of an infection with *Leptospira* spp. Six days into treatment for leptospirosis and with apparent resolution of clinical signs, there was an acute onset of severe subcutaneous and retrobulbar emphysema and dyspnoea necessitating euthanasia. A free-ranging subadult male southern sea otter (case 11) was a known and tagged individual found dead unexpectedly with no prior history of respiratory distress. Case 12 was a stranded, malnourished immature female sea otter with suspected shark bite injuries that had died overnight after rescue without signs of respiratory distress. A subadult male harbour porpoise live-stranded on a beach but died shortly afterwards without signs of external trauma (case 13).

At necropsy, tissue samples from all major organs were collected and fixed by immersion in 10% neutral-buffered formalin for a minimum of 24 h. The samples were dehydrated, embedded in paraffin wax, sectioned at 4 μm and stained with haematoxylin and eosin (HE).

3. Results

3.1. Necropsy findings

The necropsy findings and gross diagnoses are summarized in Table 1.

3.1.1. Domestic small animals

All the cats (cases 1, 2 and 3) had abundant air bubbles in the submandibular, thoracic and abdominal subcutaneous tissue (SE), in mediastinal space around the oesophagus and trachea (PM) and in the retroperitoneal space (PRP) (Fig. 1a–c). The lungs were partially collapsed (bilateral PTX) in cases 2 and 3. While the cause of air leakage was not detected for case 1, a longitudinal laceration (up to 15 mm in length) was detected on the dorsal aspect of the trachea (Fig. 1b) in both cases 2 and 3.

Similarly, all the dogs (cases 4, 5 and 6) had generalized SE affecting the cervical, thoracic and lumbar regions as well as marked PM and PRP. Cases 4 and 6 had bilateral PTX. The cause of air leakage

Table 1
Age, sex, gross lesions and cause of air leak syndrome identified at necropsy of 13 animals of various species

Case	Species	Age	Sex	PM	SE	PRP	PTX	PPC	Cause
1	Cat	7 y	M	+	+	+	–	–	Spontaneous
2	Cat	6 mo	F	+	+	+	+	–	General anaesthesia: tracheal laceration
3	Cat	8 y	F	+	+	+	+	–	General anesthesia: tracheal laceration
4	Dog	6 y	F	+	+	+	+	–	Spontaneous
5	Dog	7 y	M	+	+	+	–	–	Diffuse alveolar damage: *Leptospira* spp. infection
6	Dog	1.5 y	F	+	+	+	+	–	Lung perforation due to foreign bodies (grass awns)
7	Harbour seal	~4 mo	M	+	+	–	–	–	Lungworms (*Otostrongylus circumlitus*)
8	Harbour seal	Reproductively active adult	F	+	–	–	–	–	Obstruction of thoracic inlet by oesophageal mass (impacted bolus of fish bones)
9	California sea lion	1 y	F	+	+	–	–	–	Lungworms (*Parafilaroides decorus*)
10	California sea lion	1.5 y	M	+	+	+	_	_	Bronchopneumonia (*P. decorus*, mixed bacterial) and uraemic pneumonitis secondary to leptospiral nephritis
11	Southern sea otter	Subadult	M	+	+	–	–	–	Trauma (probably conspecific)
12	Southern sea otter	Immature	F	+	–	–	–	+	Trauma (probable shark bite)
13	Harbour porpoise	Subadult	M	+	+	+	+	–	Probable blunt force trauma

y, years; mo, months; F, female; M, male; PM, pneumomediastinum; SE, subcutaneous emphysema; PRP, pneumoretroperitoneum; PTX, pneumothorax; PPC, pneumopericardium; +, lesion present; –, lesion absent.

was not identified in case 4, although predisposing lesions were identified in cases 5 and 6. In case 5 the lesion predisposing to air leakage was severe acute interstitial pneumonia observed grossly and characterized histologically by acute diffuse alveolar damage, including hyaline membrane formation and fibrinonecrotizing alveolitis, accompanied by multifocal haemorrhages and oedema. The jaundice visible grossly was associated with histological lesions of hepatocyte dissociation, multifocal single-cell necrosis and interstitial haemorrhages. Multifocal haemorrhages were also seen in the spleen and kidney, which also had interstitial oedema and sporadic acute tubular necrosis. These findings were consistent with an ante-mortem molecular diagnosis of leptospirosis. However, immunohistochemistry on kidney, liver, spleen and lung tissues yielded negative results. In case 6, two penetrating foreign bodies (grass awns) were located in the thoracic cavity. One had perforated the caudal mediastinum and the other had penetrated the chest wall near a circular laceration in the right caudal lung lobe, leading to partial lung collapse (bilateral PTX).

3.1.2. Marine mammals

The Pacific harbour seal pup (case 7) had died from severe shark bite lacerations to the pelvis and hindlimbs. At necropsy, it also had marked bilateral cranioventral pulmonary consolidation, catarrhal tracheitis and bronchitis with a heavy burden of metastrongyle nematodes (*Otostrongylus circumlitus*) in the major airways. Air bullae were present in the interstitium of the pulmonary hilus (PIE), within the mediastinum (PM) and extending along the fascia of the neck dorsal to the trachea and oesophagus (SE) (Fig. 2a). Case 8, the adult harbour seal, had a firm mass (16 × 8 cm) of compacted fish bones that distended the oesophagus from approximately cervical vertebra C4 to the heart base as observed on radiographs. The oesophageal mucosa was ulcerated and the bolus was firmly adherent to the exposed lamina propria. There was marked emphysema of the dorsal visceral pleura and mediastinum (PM), with extension of bullous emphysema into the pulmonary interstitium (PIE) of the cranial poles of the lung lobes from the hilus (Fig. 2b).

The two California sea lions (cases 9 and 10) had a combination of SE and PM with PRP and there was also retrobulbar emphysema in case 10. The trachea, bronchi and bronchioles of case 9 were filled with viscous mucus and many small fine *Parafilaroides decorus* nematodes (Fig. 2c). The lungs had failed to collapse and there were innumerable miliary white nodules (up to 5 mm diameter) randomly distributed throughout the parenchyma of all lobes. Interstitial emphysema was particularly marked in the hilar parenchyma and around the bronchi, extending into the mediastinum and tracking cranially into the cervical fascia and subcutis. In case 10, there was marked diffuse emphysema of the oesophageal tunica adventitia extending from the pharynx to the stomach; the mediastinum was markedly expanded by large emphysematous bullae that occupied approximately 25% of the thoracic space (Fig. 3a). The left cranial and medial lung lobes were diffusely swollen and consolidated with marked interstitial oedema and on cut section, suppurative exudate was expressed from the smaller airways. *Citrobacter freundii* and *Staphylococcus* spp were isolated on aerobic culture from the cranial lung lobes. The left caudal lobe was markedly congested and oedematous and, like the other lobes, the cranial third of the lobe was consolidated. Severe subcutaneous emphysema extended from the head to the pelvis (Fig. 3b). Retrobulbar emphysema was present bilaterally with ocular proptosis. In the abdominal cavity, there was marked bilateral emphysema of the retroperitoneal space (Fig. 3c). The kidneys were moderately enlarged and on cut section the renal cortices were diffusely expanded (Fig. 3c) and pale tan. The histological renal findings were consistent with tubulointerstitial nephritis, potentially triggered by *Leptospira* spp infection.

The principal gross findings in the southern sea otter (case 11) included laceration of the skin over the larynx (conspecific bite wound) that penetrated the ventral laryngeal lamina and fractured the epihyoid and thyrohyoid bones. The fractured bone had further lacerated the sternohyoideus muscle. The subcutis adjacent to the ventral neck lacerations and fractured larynx were expanded by many coalescing air-filled bullae (SE). The laryngeal and tracheal mucosae were diffusely congested, with oedema expanding the lamina propria and blood-stained froth filling the airways. The lungs had failed to collapse and had marked interstitial to bullous emphysema that also expanded the mediastinum (PM) and parietal pleura (Fig. 4a). The second sea otter (case 12) died from a shark bite that caused numerous cutaneous and musculoskeletal lacerations with no evidence of chest penetration. At necropsy there was also diffuse pulmonary congestion and cervical and mediastinal bullous emphysema (PM) as well as extension of air into the pericardial sac (PPC) (Fig. 4b).

The harbour porpoise (case 13) was in an excellent nutritional state at necropsy with no significant external lesions. The subcutis and skeletal muscle fascia of the trunk from the head to the peduncle were expanded by numerous air pockets that ranged from a few millimeters to 3–4 cm in diameter. The lungs were atelectatic (PTX) (Fig. 4c) and peripherally the visceral pleura was expanded by many coalescing air-filled bullae. The mediastinum

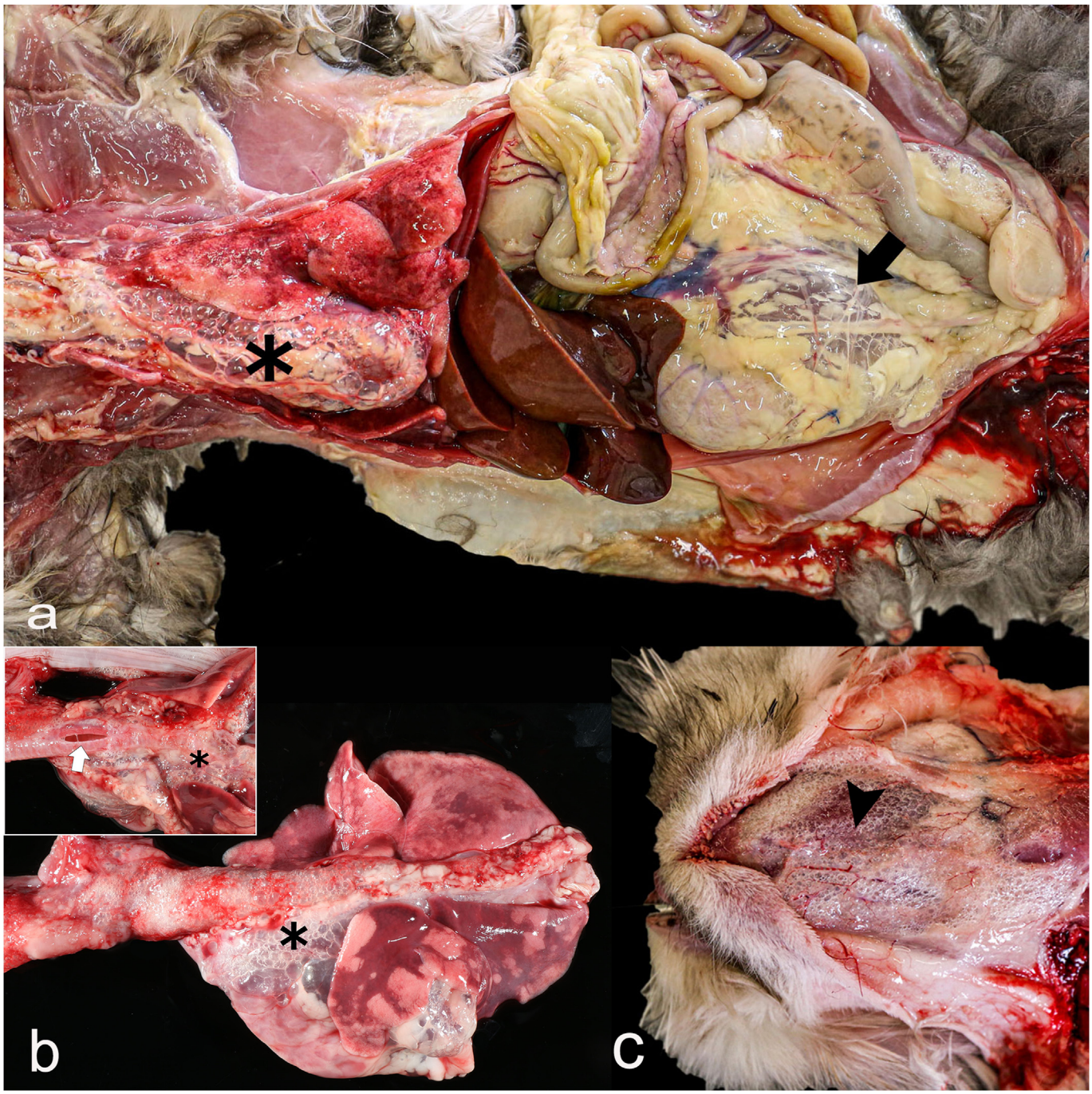

Fig. 1. (**a**) Cat, case 1. Pneumomediastinum and pneumoretroperitoneum. Gas bubbles in mediastinum (*) and retroperitoneal space (arrow). (**b**) Cat, case 2. Pneumomediastinum with abundant gas bubbles in cranial mediastinum and around trachea (*). Inset: tracheal laceration (arrow) and pneumomediastinum (*). (**c**) Cat, case 3. Subcutaneous emphysema with numerous gas bubbles in submandibular subcutaneous tissue (arrowhead).

and thoracic rete mirabile were also expanded by numerous air bubbles and bullae up to 4 cm in diameter (PM). In the abdominal cavity, there were numerous bullae on the visceral surface of the diaphragm and the retroperitoneum was expanded by air-filled bullae (PRP) that surrounded both kidneys and the adrenal glands (Fig. 4d). The omentum contained hundreds of air-filled pockets up to 2 cm in diameter (Fig. 4d).

4. Discussion

Emphysema and various forms of air entrapment (SE, PM, PRP and PTX), equivalent to ALS in humans, have been described in cats, dogs, horses, cows, goats and marine mammals, mainly pinnipeds (Supplementary Table 1). Nevertheless, the concept of ALS has not been adopted generally in the veterinary literature. In this study a

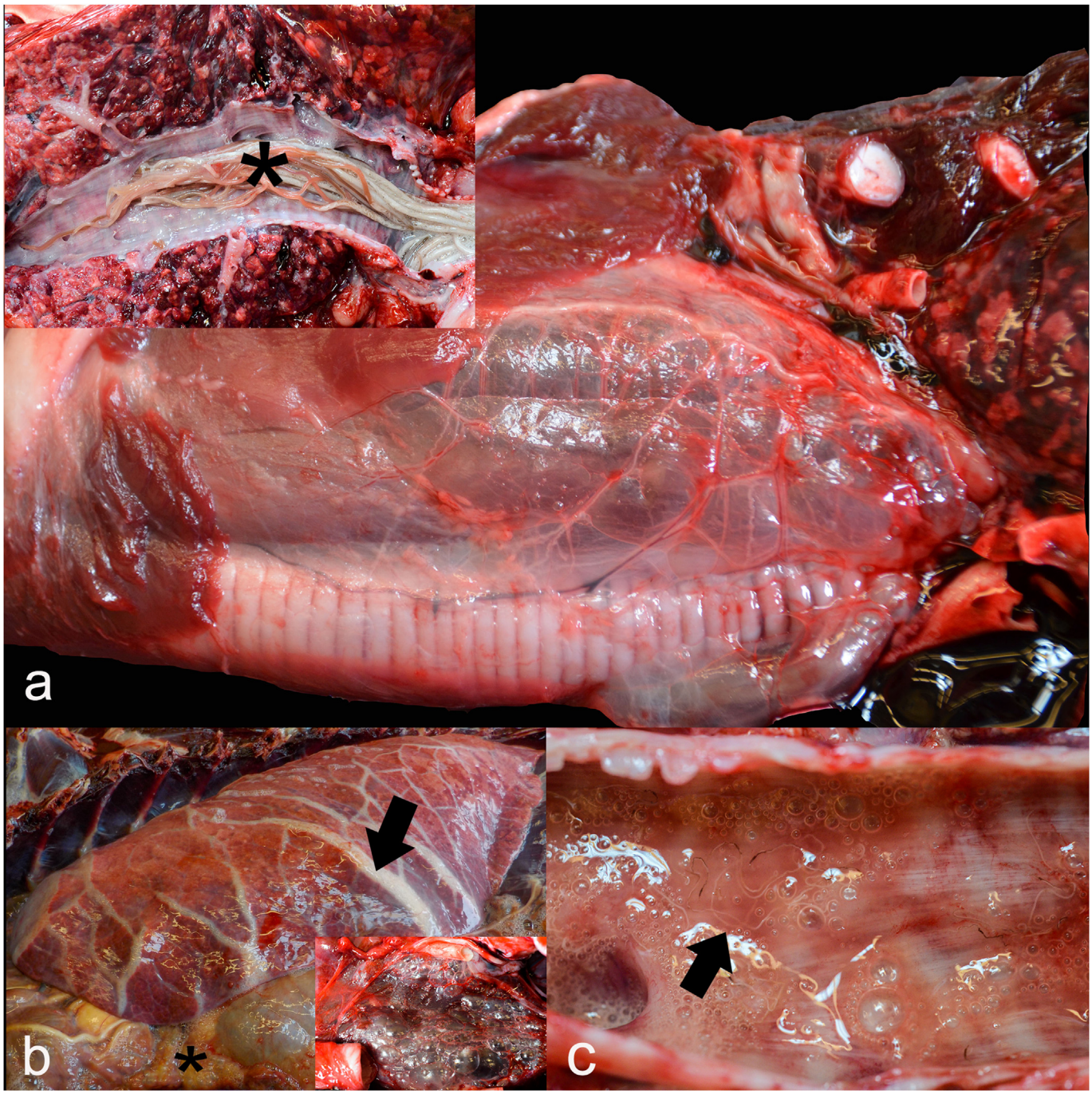

Fig. 2. (**a**) Pacific harbour seal, case 7. Pneumomediastinum with generalized expansion of cranial mediastinum due to presence of large gas bubbles (PM). Inset: primary bronchus obstructed by *Otostrongylus circumlitus* nematodes (*). (**b**) Harbour seal, case 8. Interstitial pulmonary emphysema (arrow) and pneumomediastinum with abundant air bullae in ventral mediastinum (* and inset). (**c**) California sea lion, case 9. Section of primary bronchus has moderate catarrhal bronchitis with numerous *Parafilaroides decorus* nematodes (arrow).

parallel classification of ALS is proposed in the context of veterinary pathology, mirroring the approach used in human medicine, which takes account of iatrogenic, secondary and spontaneous causes [1,2,6]. This classification is based on carefully selected cases encompassing diverse mammalian species, along with an exhaustive review of ALS across different mammalian species.

In general terms, this aetiological classification relies on the identification of underlying lesions that initiate the accumulation of air in tissues or spaces that are typically not infiltrated by air. Iatrogenic causes in general are linked with surgical, diagnostic or parenteral interventions, both intrathoracic and extrathoracic, such as endoscopy, tube feeding or gastric boluses. Secondary ALS can stem from trauma, non-infectious primary pulmonary conditions or infectious diseases affecting the lung parenchyma or extrathoracic tissues [5,6,10]. Spontaneous cases are usually diagnosed when a distinct aetiology cannot be identified.

Irrespective of the subtype of ALS, common clinical manifestations in animals encompass respiratory distress, sometimes accompanied by subcutaneous distension, crepitation and pain. Consequently, these clinical signs warrant consideration of ALS.

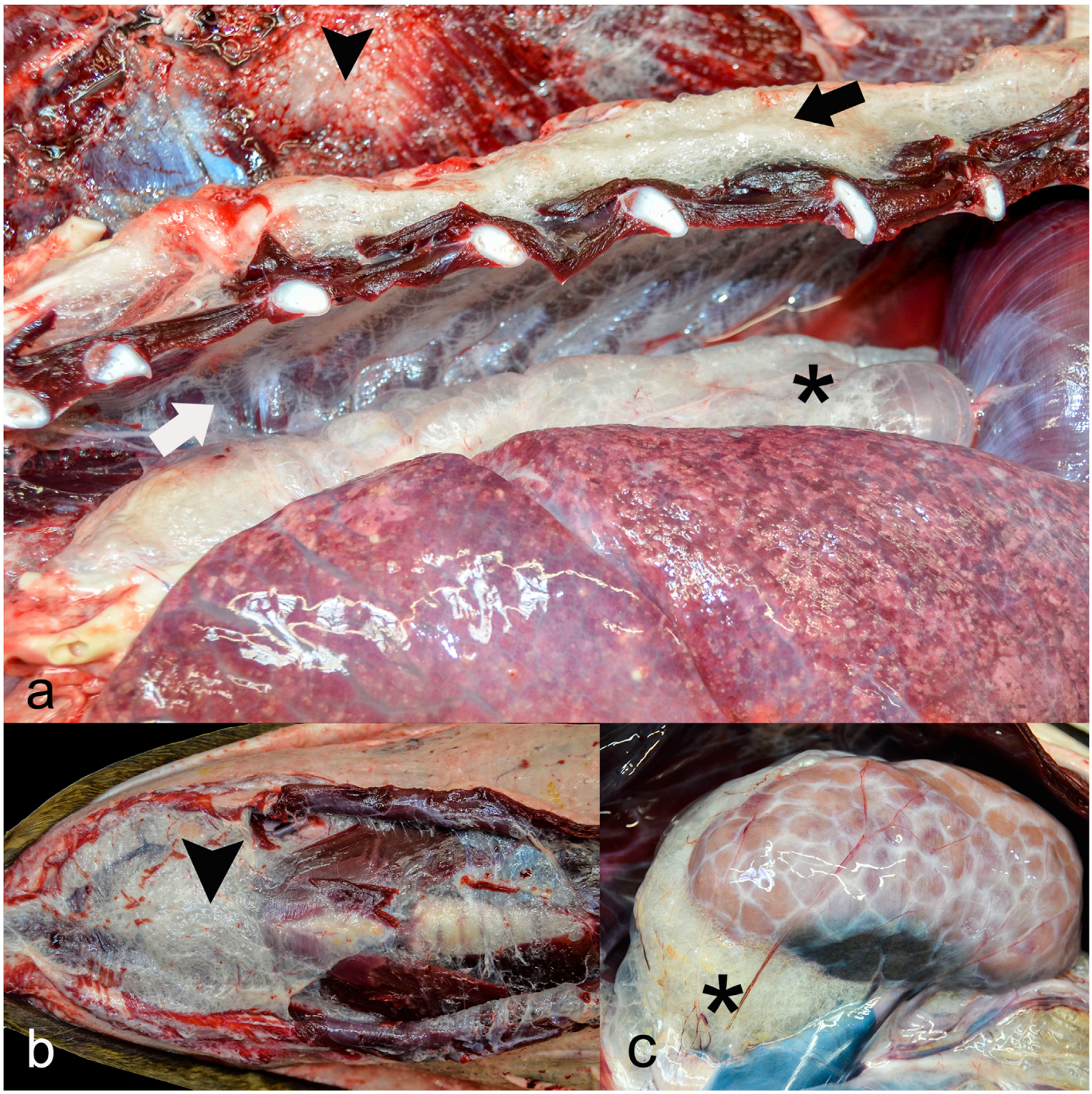

Fig. 3. California sea lions. (**a**) Case 10. Generalized mediastinal emphysema (*) within pectoral muscle (arrowhead), dissecting between intercostal and pectoral muscle (black arrow) and beneath parietal pleura (white arrow). Lungs swollen and consolidated with multifocal white nodules consistent with granulomatous verminous (*Parafilaroides decorus*) bronchopneumonia. (**b**) Case 10. Fascial subcutaneous emphysema extending from cranium to thoracic inlet (arrowhead). (**c**) Case 10. Emphysema within retroperitoneum (*). Moderately enlarged and diffusely pale kidney consistent with interstitial nephritis.

Among the four selected study cases that included ante-mortem imaging, the presence of entrapped air was confirmed by radiography. It is worth noting that post-mortem imaging could be beneficial to pathologists, although the impact of autolysis on the presentation at necropsy should be recognized.

Consistent with findings in human patients, animals commonly exhibit a predominant manifestation of combined forms of air entrapment, irrespective of the underlying cause of ALS. This pattern was evident in the necropsy findings in this study. Notably, PM emerged as the prevailing ALS presentation across all mammalian species, often accompanied by SE and PRP in dogs and cats, which is consistent with the established literature [11]. Although understanding of the prevalence of this particular ALS combination across diverse mammalian species is limited, van den Broek [7], through his study on canine mediastinal anatomy, provided an explanation for cases involving SE and PRP arising as a result of PM in dogs. This viewpoint corresponds with the interconnectedness of the mediastinum with the retroperitoneum and subcutaneous fascia, which collectively contribute to this combined ALS presentation.

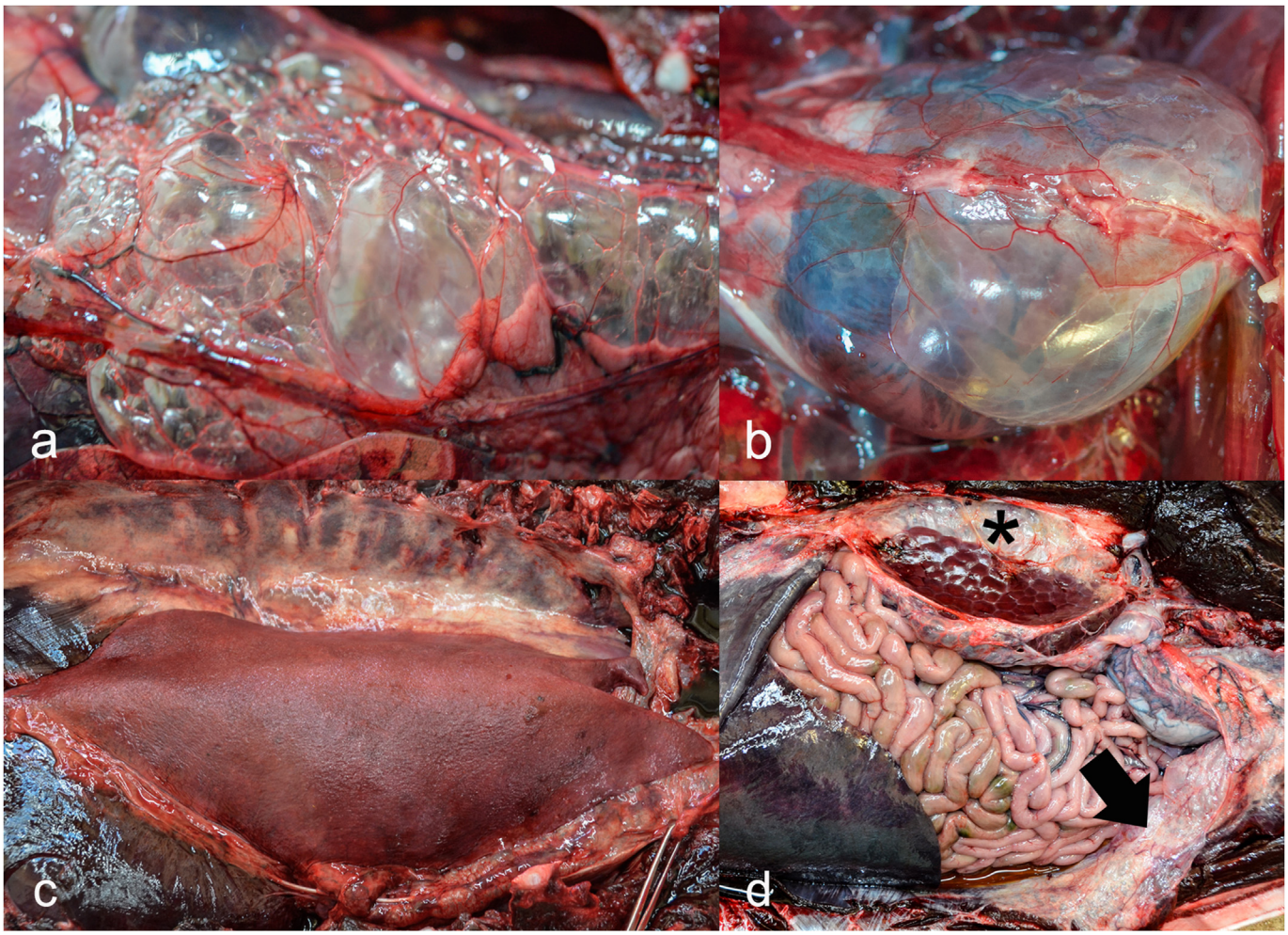

Fig. 4. (**a**) Southern sea otter, case 11. Mediastinum and caudal cervical region expanded by large air-filled bullae. (**b**) Southern sea otter, case 12. Pneumopericardium and pneumomediastinum. (**c**) Harbour porpoise, case 13. Pulmonary atelectasis secondary to pneumothorax. (**d**) Case 13. Abdominal cavity with pneumoretroperitoneum (*) and numerous air-filled pockets throughout omentum (arrow).

Conversely, PTX was infrequently identified in necropsies across all selected animals, while PPC was notably absent in most species. These findings align with previous findings in humans and animals, but not in horses, in which the prevalent ALS presentation involves the combination of PM with bilateral PTX and SE [11–14]. This specific presentation in horses can be attributed to the incomplete structure of the equine mediastinum, which is characterized by the presence of fenestrations in the caudal and ventral portions of the mediastinal pleura. These anatomical features support the investigations of Macklin and Macklin [15] and van den Broek [7] who found that the mediastinum-to-visceral pleura communication contributes to the occurrence of PTX in cases of primary PM. Although comparable descriptions of mediastinal anatomy are lacking for cats, pinnipeds, sea otters and porpoises, a plausible inference is that their mediastinal configuration resembles that of dogs, given the uniform clinical and pathological ALS presentation in these species. However, a comprehensive exploration of comparative mediastinal anatomy might uncover distinct ALS presentations and combinations across different species, necessitating further research.

Consistent with prior research, cats display a similar prevalence across the three classifications of ALS [6]. The primary contributor to iatrogenic ALS in cats was associated with tracheal damage subsequent to general anaesthesia and endotracheal intubation, coupled with positive ventilation pressure. However, pericardiocentesis resulted in this form of ALS less frequently [6]. This is consistent with two cases in this series, in which tracheal lacerations arising from surgical procedures led to iatrogenic ALS. In contrast, no predisposing lesions were detected in the third selected cat despite a history of previous surgery. Consequently, it was diagnosed as spontaneous ALS, a phenomenon also commonly reported in this species, albeit with loose associations to exercise and sudden vomiting [6]. Finally, secondary ALS was generally related to foreign body penetration or traumatic pulmonary injury and less commonly to infectious and non-infectious primary pulmonary disorders such as feline herpesvirus pneumonia or neoplasia [2,16].

Unlike cats, the most commonly reported cause of ALS in dogs is secondary ALS mainly associated with pulmonary trauma and/or cervical injuries due to animal bites and foreign bodies [17]. This is consistent with the findings in one dog in the present series, in which lung and mediastinal laceration were associated with grass awn migration. Other reported causes of secondary ALS in dogs due to traumatic injuries are bullets, vehicle collisions, blunt trauma, choke chain injury, pulmonary-pericardial communication, vascular damage and alveolar rupture associated with coughing and bronchospasm [6,18–22]. Secondary ALS associated with infectious and non-infectious primary pulmonary diseases has been described less frequently in dogs but cases include *Pneumocystis carinii*

pneumonia, one report of PPC secondary to infectious pericarditis after oesophageal foreign body migration, primary fibrosing interstitial pneumonia, primary pulmonary emphysema with rupture of bullae and congenital lobular emphysema [23–27]. Interestingly, one of the canine cases in this series had secondary ALS due to acute respiratory distress syndrome (ARDS) apparently following a systemic infection with *Leptospira* spp, which is not a commonly reported cause of ALS in animals. ARDS has been described as a cause of ALS in humans associated with systemic infections such as SARS-CoV-2 [28]. In these cases, the pathogenesis of ALS is not well understood, but could be related to an imbalance between leucocyte-derived proteases and antiproteases released during the inflammatory reaction or to uraemic pneumonia in cases of leptospirosis [29]. In both scenarios, weakened alveolar septa can become susceptible to stress-induced failure caused by fluctuating pressure during ventilation, leading to pneumomediastinum in accord with the Macklin effect [4]. Finally, spontaneous ALS, as observed in one of our cases, is considered the least frequent category in dogs, with only a few reports [30,31].

In pinnipeds and small odontocetes, the most frequently reported types of ALS are PM, SE and, less frequently, PRP and PPC secondary to pulmonary infectious diseases such as viral pneumonia (eg, phocine distemper virus or influenza A virus) and lungworm infection. ALS lesions have been reported most frequently in free-ranging harbour seals and harbour porpoises and, occasionally, in grey, harp and hooded seals [32–38]. Massive pulmonary parasitism is a frequent cause of respiratory dysfunction and death in juvenile pinnipeds and odontocetes [39]. This is consistent with ALS in two of our cases, a harbour seal pup and a yearling California sea lion that had severe parasitic bronchopneumonia leading to secondary ALS. While the precise mechanism of ALS development resulting from pulmonary parasitism is unclear, potential factors include direct alveolar and/or bronchiolar wall damage induced by parasites, inflammation-triggered effects or secondary outcomes arising from goblet cell hyperplasia. This hyperplasia, in conjunction with the presence of viscous mucus and adult nematodes in the airways, might contribute to airway obstruction/occlusion [40]. These scenarios lead to the movement of air into the mediastinum, a phenomenon in accord with the Macklin effect [4]. The second sea lion was euthanized due to leptospirosis leading to secondary ALS and sudden onset subcutaneous and retrobulbar emphysema, PM and PRP. In this case, ALS could have originated similarly to dogs with leptospirosis in this series. However, it was further aggravated by potential alveolar damage arising from either the mechanical impact of parasites or the influence of inflammatory agents, attributed to the concurrent presence of secondary bacterial infection and pulmonary metastrongyles. The accumulation of inflammatory exudate in the airways can lead to intermittent airway obstruction, a situation informally described as a 'stop-go valve' effect. This is not a recognized medical term, but the phenomenon could contribute to the development of ALS in certain types of pneumonia that cause airway blockages and inflammation.

In some pinnipeds and small odontocete cetaceans, extra-pulmonary traumatic injury may provide a mechanism for the development of secondary ALS. For the aged adult harbour seal with an oesophageal impaction in this case series, the deep transmural ulceration was the likely portal of entry for air into the mediastinum. The harbour porpoise was a case of sudden death that, based on epidemiological factors (species, location and time), was suggestive of interspecific aggression by a larger odontocete, the bottlenose dolphin (*Tursiops truncatus*) [41]. In this animal, blunt force trauma to the thorax and abdomen with a closed glottis likely resulted in air leakage into the mediastinum and from there to the thoracic cavity, retroperitoneum and subcutis.

In southern sea otters, pulmonary lesions that include interstitial emphysema and oedema were reported as the cause of death in 7% (40/560) of cases in a 15-year mortality study [42]. Fight trauma accounted for 14% (46/329) of male deaths while overall, shark bites killed 28% (160/560) of all otters. The pathogenesis was not always known but in the two cases in the present series, trauma either from predatory attack or conspecific fighting was the mechanism involved in development of secondary ALS. For both animals, PM and SE were the primary presentations but one otter also had PPC, which was the only example in this series. In general, leakage of air into the pericardium is rare in both humans and domestic animals and is generally a benign condition. Nevertheless, it has a poor prognosis because of the potential for fatal cardiac tamponade [11,43].

Diverse manifestations of air leakage have been documented in horses, cattle and goats, consequently warranting consideration of ALS within these species [12–14,44–48]. Consistent with previous reports, most secondary ALS cases in horses have been associated with penetrating thoracic or axillary injuries, resulting in air entrapment within the subcutaneous tissue [SE] and subsequent PM, bilateral PTX and, rarely, PRP [49]. Additionally, occurrences following blunt force trauma and rib fractures were less common and were predominantly observed in neonatal foals during parturition. A few occurrences of spontaneous and iatrogenic ALS have also been documented in horses [50,51], including one that followed tracheal or oesophageal perforation or procedures such as sinoscopy, sternal bone marrow aspiration and tracheostomy [13,51–53].

In cattle, ALS is a rare syndrome most commonly observed *post partum*, due either to exacerbation of pre-existing chronic pulmonary disease or of exertion during parturition [54,55]. Most cases were classified as secondary to pulmonary infection with bovine ephemeral fever virus, bovine respiratory syncytial virus, massive infestation by *Dictyocaulus viviparous* or paralytic rabies, or as a complication of bronchopneumonia [55,56]. The mechanism of ALS in rabies is unknown but it might be associated with violent spasms of the pharynx and larynx that cause acute and temporary obstruction of the airways, leading to alveolar rupture under a brief period of increased pressure [54]. Non-infectious primary lung diseases have also been implicated in the pathogenesis of bovine secondary ALS including bovine fog fever and intoxication by mouldy sweet potatoes contaminated with *Fusarium solani* as a cause of pulmonary and subcutaneous emphysema [29]. Finally, rare cases of secondary traumatic ALS were described in a bovine animal with a foreign body perforation and in a goat following a dog bite [55,57].

5. Conclusion

The term ALS should be used more frequently by veterinary pathologists to refer to a suite of lesions related to the accumulation of air in spaces that normally do not contain air. The most frequent combination of these lesions in animals is PM with SE, followed by PRP, PTX and, rarely, PPC. Depending on the predisposing causes, ALS in animals may be classified as iatrogenic, secondary or spontaneous. The diagnosis of ALS should include the clinical history and signs, diagnostic imaging and lesions observed at necropsy, but determination of the exact aetiopathogenic mechanisms may be challenging as specific anatomical features and physiological phenomena may vary among species.

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Declaration of competing interests

The authors declared no conflicts of interest in relation to the research, authorship or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcpa.2024.04.005.

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