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REGULAR ARTICLES

The first identification of contagious caprine pleuropneumonia (CCPP) in sheep and goats in Egypt: molecular and pathological characterization

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Abstract

Contagious caprine pleuropneumonia (CCPP) is one of the most fatal and contagious diseases of goats. To date, the occurrence of CCPP in Egypt has not been reported. During the period from 2017 to 2018, 200 goats and 400 sheep from Matrouh Governorate (Al Alamein and El Hammam cities) were suspected to have CCPP; animals were examined to confirm the presence of CCPP infection as well as the epidemiological status, clinical features, and molecular and histopathologic characteristics of lung tissues. Additionally, a treatment trial was performed to assess the efficacy of anti-mycoplasma therapy in the treatment of clinical cases of this disease. The occurrence of CCPP was 32.5% and 5% in goats and sheep, respectively, while case fatality was 30% and 8% in goats and sheep, respectively. The clinical forms of CCPP in both sheep and goats varied from per-acute to acute or chronic cases. Histopathological analysis of lung tissues from dead cases (either sheep or goats) revealed different stages of broncho- and pleuropneumonia ranging from per-acute to acute or chronic stages. Lung tissues showed severe congestion of interalveolar capillaries, flooding of alveoli and bronchi with a fibrinous exudate, a high degree of pleural thickening, and multifocal areas of necrosis that were sometimes sequestered in the fibrous capsule. Isolation of *Mycoplasma capricolum* subspecies *capripneumoniae* (Mccp) was confirmed in all dead cases by agar and broth culture methods and polymerase chain reaction. The treatment trial revealed that the marbofloxacin and spiramycin groups had a higher cure rate (70%) than the oxytetracycline group (40%) and a lower fatality rate (30%) than the oxytetracycline group (60%). Conclusively, infection with CCPP in goats and sheep is considered to be novel for Mccp in Egypt, where this species is considered to be the main pathogen in goats, not in sheep. Additionally, it could be concluded that treatment may be effective only if given early. Further comprehensive surveys are required to investigate the risk of CCPP in goats and sheep in all Egyptian governorates.

Keywords CCPP · *Mccp* · Pathologic lesions · Oxytetracycline · Sheep · PCR

Introduction

Respiratory diseases are common illnesses in all animal species worldwide. In small ruminants, respiratory infections are among the major causes of mortality and the subsequent economic loss (Sandip et al. 2014). In the USA, the respiratory disease-associated economic loss was estimated to be more than one billion dollars (Nicolas et al. 2008). Interestingly, infectious respiratory disorders of sheep and goat are involved in 5.6% of the total small ruminant diseases and represent approximately 50% of the global death rate (Kumar et al. 2014).

Contagious caprine pleuropneumonia (CCPP) is a highly contagious fatal disease of caprines that can occur in both domestic and wild-breed goats (Nicholas 2002; Arif et al. 2007; Ostrowski et al. 2011). CCPP was reported for the first time in Algeria in 1873 (McMartin et al. 1980), where it is considered to be devastating disease of goat that causes great economic loss in the global goat industry (Bascunana et al. 1994).

To date, a great number of outbreaks have occurred in countries where this disease was not as prevalent previously.

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It is reported that nearly 478 outbreaks were recorded in Iran from 2006 to 2007 (affecting 16,000 goats). In addition, 38 outbreaks were recorded in Ethiopia, and 600 outbreaks were recorded in Oman from 2008 to 2009, affecting 30,000 goats (OIE 2008, 2009; Yatoo et al. 2019). In 2009 alone, several CCPP outbreaks occurred, including in Yemen (12 outbreaks affecting 800 goats), Tanzania (10 outbreaks affecting 200 goats), Tajikistan (4 outbreaks affecting 166 goats), and Mauritius (affecting 300 goats) (Srivastava et al. 2010; EFSA AHAW Panel et al. 2017). However, in Pakistan, from 2008, frequent CCPP outbreaks have been noted by Awan et al. (2009, 2010a, 2010b, 2012). In Africa, the spread of CCPP occurred from Central and Eastern Africa to other parts (AU-IBAR 2011). The incidence of CCPP has been reported in seven countries of Africa (Lorenzon et al. 2002; Yatoo et al. 2019) and in goat populations of more than 40 countries.

CCPP is classically characterized by unilateral gross consolidation of lungs, pleural fluid accumulation, and pleural adhesion; however, the main microscopic lesions usually involved septal peribronchiolar fibrosis and fibrinous pleuritis (Rurangirwa and McGuire 2012; Hussain et al. 2012).

CCPP may manifest in per-acute, acute, or chronic forms. In the per-acute form, death occurs suddenly within 24–72 h without premonitory (respiratory) signs (MacOwan and Minette 1976; Samiullah 2013a, 2013b). In the less acute or chronic form, and in mildly affected or relatively resistant animals, the disease is characterized by dyspnoea, high fever, coughing, nasal discharge, lying down, thorax pain, loss of body condition, and heavy morbidity (up to 100%) and mortality (80–100%) (Rurangirwa and McGuire 1996; Radostitis et al. 2009; OIE 2014). In clinical cases, abdominal respiration with accelerated and painful (pleurodynia) respiratory movements is observed. Terminal stages are characterized by recumbency, abducted elbow, and extended neck (Hussain et al. 2012; Tharwat and Al-Sobayil 2017).

Several types of vaccines and antibiotics have been described to control and treat the disease. However, only one case study showed the effectiveness of streptomycin in the treatment of natural and experimental CCPP-infected goats; the authors illustrated that infected goats recovered and became completely immune to the disease on the third day of treatment (Rurangirwa and McGuire 2012). Additionally, the effectiveness of danofloxacin (Ozdemir et al. 2006) and long-acting oxytetracycline (Giadinis et al. 2008) have been described; oxytetracycline has been shown to eliminate morbidity, mortality, and further spread of CCPP. The aim of the current study was to isolate, for the first time, Mccp from sheep and goats in Egypt. We sought to examine the epidemiological status, clinical features, and molecular and histopathologic characteristics of CCPP in lung tissues and to investigate the efficacy of anti-mycoplasma therapy in the treatment of clinical cases of the disease.

Materials and methods

Animals

During the period from 2017 to 2018, 200 goats and 400 sheep from Matrouh Governorate (El Hammam and Al Alamein city farms) were clinically examined to examine the epidemiological status and clinical characteristics of CCPP. The examined animals comprised adult goats and sheep of both sexes with a history of anorexia, coughing, and nasal discharge.

Isolation and identification on agar and broth media

Postmortem samples comprising lung tissues and pleural fluid were collected from carcasses exhibiting gross pathology typical of CCPP. Samples were sent cooled to the laboratory of the Infectious Disease Department (Faculty of Veterinary Medicine, Alexandria University) in an ice bag (4 °C). Growth and isolation of *Mycoplasma* were performed using *Mycoplasma* agar and broth media (M0535-250G, Sigma Aldrich, USA). Selective isolation of *Mycoplasma* species was performed by incubation for 7 days with agar medium (CC1A, Mycoplasma Experience Ltd. Product), allowing development of red Mccp colonies as described previously by Samiullah (2013a, 2013b).

Detection and identification by polymerase chain reaction

As previously described by Woubit et al. (2004), positive cultures in liquid broth (30 goat and 8 sheep cultures) were centrifuged at 12,000×*g* for 20 min, and the pellet was resuspended in 300 μl of water. The bacterial suspension was then treated with 300 μl of TNES buffer (20 mM Tris (pH 8.0), 150 mM NaCl, 10 mM Tris-ethylenediamine tetra-acetic acid, 0.2% sodium dodecyl sulfate) and proteinase K (200 μg/ml) and kept at 56 °C for 1 h. The suspension was heated at 95 °C for 10 min to inactivate proteinase K. The polymerase chain reactions (PCRs) were performed in a TC-512 temperature cycling system in a reaction volume of 50 μl, containing 5 μl of 10× PCR buffer (750 mM Tris-HCl (pH 8.8), 200 mM (NH4)2SO4, 0.1% Tween 20), 5 μl of 25 mM MgCl2, 250 μM each deoxynucleotide triphosphate, 1.25 U Taq DNA polymerase, 20 pmol of each primer, and 25 ng of template DNA. The Mccp-specific primers Mccp-spe-F (5′-ATCAT TTTTAATCCCTTCAAG-3′) and Mccp-spe-R (5′-TACT ATGAGTAATTATAATATATGCAA-3′) were employed.

The Mccp-specific PCR was performed as follows: an initial denaturation step at 94 °C for 2 min; amplification with 35 cycles of denaturation at 94 °C for 30 s, annealing at 47 °C for 15 s, and extension at 72 °C for 15 s; and a final extension step

at 72 °C for 5 min. The amplified products were detected by staining with ethidium bromide (0.5 μg/ml) after electrophoresis at 80 volts for 2 h in 1.5% agarose gels. PCR products with a molecular size of 316 bp were considered indicative of Mccp.

Histopathology

Upon necropsy, representative lung tissues were collected from the interface between consolidated and unconsolidated areas, fixed in 10% buffered formalin solution, embedded in paraffin blocks, sectioned at 3–5 μm thick sections and routinely stained with hematoxylin and eosin (HE) according to Bancroft and Gamble (2013).

Treatment trials

The therapeutic treatment of CCPP cases in this study was performed by dividing the animals to be tested into three different groups to determine the efficacy of anti-mycoplasma therapy on the animal cure rate. Animals selected for this trial were treated immediately after the appearance of clinical signs, which suggested that all the animals tested were at a similar stage of disease (acute stage). Complete recovery of clinical signs is considered to be an indicator of successful treatment. Drugs were chosen according to pharmacological action and availability in Egypt. In the first group, 10 animals were injected with 10% Marbocyl, containing 10% marbofloxacin (Vetoquinol, France), at 1 ml/50 kg B.wt I/M for 3 successive days. In the second group, 10 animals were administered 50 mg/ml spiramycin (Spirovet® Ceva Sante Animale Egypte, 1 ml/20 kg B.wt I/M for 2 successive days). In the last group, 10 animals were treated with 200 mg/ml Alamycin LA (21.6% w/v oxytetracycline dihydrate, equivalent to 20.0% w/v oxytetracycline; Norbrook Laboratories, Northern Ireland).

Results

As illustrated in Table 1, according to the clinical examination of the total of 600 animals, the reported occurrence of CCPP in the goat population was estimated to be 65 goats out of 200 (32.5%). However, in sheep, only 20 cases were recorded out of the 400 examined animals, with an incidence of 14.16%. In addition, the case fatality was recorded as 30 goat cases and 8 sheep cases, with fatality percentages equal to 46.15 and 40%, respectively. The total occurrence of CCPP in the examined small ruminant population was 85 cases out of 600 (14.16%), while the total case fatality was 38 cases out of 85 infected cases (44.7%).

As shown in Table 2, clinical characterization of CCPP-infected animals revealed the presence of three different stages of infection: per-acute, acute, and chronic. Table 2 shows the clinical features and postmortem lesions of different detected stages. In the per-acute form, 9 per-acute cases suddenly died (5 goat and 4 sheep), and the lungs of these animals showed marked lung marbling (Fig. 1a). However, 30 animals in the acute stage of the disease suffered many clinical manifestations, including fever (42 °C), coughing, dyspnoea, labored respiration, copious nasal discharge, and corneal opacity (Fig. 1b); 20 goats and 2 sheep died within 9 days. The postmortem lesions in these animals showed lung marbling, straw-colored exudate within the thoracic cavity, and thickening of interlobular septa. Moreover, 44 animals showed a chronic stage of disease, exhibiting a non-feverish condition, coughing, emaciation, and stunted growth; 5 goats and 2 sheep died after 40 days (not responding to treatment). Sequestra (Fig. 1c) and adhesions between the lungs and pleurae were detected upon postmortem examination of animals chronically infected with CCPP.

With regard to selective isolation of mycoplasma on *Mycoplasma* agar and broth media, the characteristic red colonies of Mccp were observed in 100% of the cultured samples (30 goats and 8 sheep), indicating that *Mycoplasma* might have been the leading cause of death in these animals.

A total of 38 culture-positive isolates were confirmed via group-specific PCR as belonging to the *Mycoplasma* genus; these isolates produced specific bands with a molecular size of 280 bp. In the Mccp-specific PCR amplification, 30 of the goat isolates and 8 of the sheep isolates (all lung samples) produced positive products with an approximate molecular size of 316 bp (Fig. 2).

Pathologic examination of lung tissues from CCPP-infected animals revealed different stages of inflammation ranging from per-acute to acute, sub-chronic, or chronic broncho- and pleuropneumonia (Fig. 3). Severe congestion of interalveolar capillaries with flooding of alveolar spaces and bronchioles with serofibrinous or fibrinous exudate and acute inflammatory cells were evident in per-acute and acute infected tissues (Fig. 3a, b). Examination of pleurae in different cases revealed that the visceral layer of the pleura was distended by a serofibrinous exudate, while the parietal layer showed fibrous tissue organization admixed with inflammatory infiltration (Fig. 3c).

Table 1 The occurrence and case fatality of CCPP in goat and sheep populations

No. of animals	Occurrence		Case fatality	
	No.	%	No.	%
200 goats	65	32.5	30	46.15
400 sheep	20	5	8	40
Total = 600	85	14.16	38	44.7

Table 2 The clinical forms of CCPP in different stages of the disease

Forms of CCPP	Clinical features	Postmortem lesions
Per-acute (9 cases)	1. 5 goats and 4 sheep suddenly died within 2 days	1. Severe lung marbling
Acute (30 cases)	1. Fever 41 °C	1. Lung marbling
	2. Coughing, dyspnoea, and labored respiration	2. Straw-colored exudate in thoracic cavity
	3. Copious nasal discharge	3. Thickening of interlobular septa
	4. Corneal opacity	
	5. 20 goats and 2 sheep died within 9 days	
Chronic (44 cases)	1. No fever	1. Adhesion between lungs and pleura
	2. Coughing	2. Sequestrum
	3. Emaciation and failure to grow	
	4. 5 goats and 2 sheep died after 40 days (not responsive to treatment)	

The interlobular septum was distended by a serofibrinous exudate, congested blood vessels, and inflammatory infiltrates (Fig. 3d). Additionally, necrosis and fusion of the bronchial epithelium with extensive peribronchial and subepithelial infiltration of lymphocytes was also observed (Fig. 3e). Additionally, interstitial lymphoplasmacytic infiltrations and multifocal infiltrations of lymphocytes in the form of follicle-like aggregates in the peribronchial and perivascular areas were observed (Fig. 3f), with mild vasculitis and formation of intravascular thrombi of adjacent blood vessels observed in subchronically and chronically infected animals (Fig. 3g). In addition, activation of intra-alveolar and intra-bronchial macrophages was described in lung tissues from chronically infected animals (Fig. 3h). Formation of multifocal areas of caseous necrosis as a result of vasculitis and thrombus formation was noticed; these necrotic areas contained eosinophilic necrotic tissue, necrotic neutrophils, and cellular debris and were surrounded by a zone of inflammatory cells and encapsulated in thick fibrous tissue capsules (Fig. 3i, j).

Treatment trials with three different types of antimycoplasma drugs revealed similar results in groups treated with marbofloxacin and spiramycin (recovery of 7 animals and death of 3 animals, with a cure rate of 70%). However, animals treated with oxytetracycline showed the lowest cure rates (40%), with a mortality rate of 60% (Table 3).

Discussion

CCPP is one of the most dangerous contagious respiratory diseases of goats. Fatality associated with CCPP is usually frequent; morbidity and mortality rates might reach 100% in some flocks. Thus, there is enormous economic loss associated with CCPP, particularly in endemic regions, including Africa, Asia, and the Middle East (Bölske et al. 1995a, 1995b).

In the current study, 200 goats and 400 sheep were suspected to be infected with Mcpp and were examined clinically to confirm the presence of CCPP. The occurrence of CCPP was 32.5% and 5% in goats and sheep, respectively, while case fatality was 30% and 8% in goats and sheep, respectively. The occurrence and case fatality of CCPP in sheep observed here are considered to be a new record for *Mccp* in Egypt, where this species is considered to be the main pathogen in goats, not in sheep. Our findings confirm the early findings of Litamoi et al. (1990, 1990), Bölske et al. (1995a, 1995b), and Shiferaw et al. (2006a, 2006b) who reported the occurrence of *Mccp* in sheep but less extent than in goat. On the contrary, in Pakistan, the causative agent of CCPP was isolated from only sick goats in the Pashin District of Balochistan (Awan et al. 2012). With regard to the clinical findings and postmortem lesions of CCPP-infected animals,

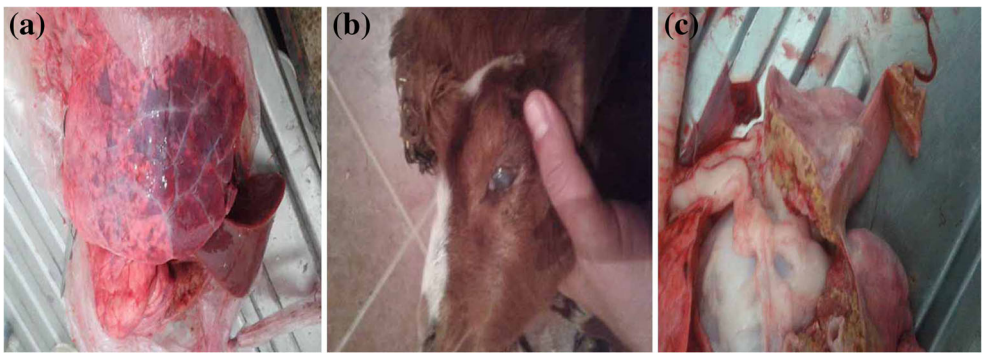


Fig. 1 Representative graphs for postmortem gross examination of CCPP-infected animals. **a** Lung from per-acute CCPP-infected animals showed marked marbling. **b** Acute CCPP-infected animals showed corneal opacity. **c** Lungs from animals chronically infected with CCPP showed sequestrum formation

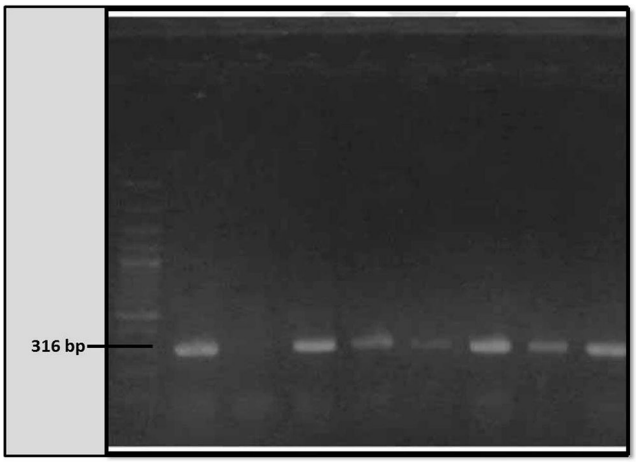


Fig. 2 Agarose gel electrophoresis of *Mycoplasma capricolum* subspecies *capripneumoniae*-specific polymerase chain reaction products. *M*, molecular weight marker (100 base-pair deoxyribonucleic acid ladder, SM0321). Lanes 1 to 8: lane 1, control positive result with a culture of *Mycoplasma capricolum* subspecies *capripneumoniae*; lane 2, negative control with water as a template; lanes 3 and 4, positive results obtained from sheep samples; and lanes 5, 6, 7, and 8, positive results obtained from goat samples (316 bp)

Fig. 3 Representative photomicrographs of lung tissues from CCPP-infected goats and hematoxylin and eosin (HE)-stained sections. **a** Severe congestion of interalveolar capillaries with flooding of alveolar spaces (arrows) and bronchioles (asterisks) with serofibrinous or fibrinous exudate and acute inflammatory cells. **b** Magnification of **a** showing fibrinous and inflammatory exudate within the bronchiolar lumen (asterisk). **c** The visceral layer of the pleura (P) is distended by a serofibrinous exudate, while the parietal layer shows fibrous tissue organization admixed with inflammatory infiltration. **d** The interlobular septum (asterisks) was distended by serofibrinous exudate, congested blood vessels (arrow), and inflammatory infiltrates. **e** Extensive peribronchial and subepithelial infiltration of lymphocytes (asterisks), with mild vasculitis in adjacent blood vessels (arrow). **f** Interstitial lymphoplasmocytic infiltrations (arrows), with formation of intra-vascular thrombi of adjacent blood vessels. **g** Intra-alveolar (thin arrows) and intra-bronchial (asterisk) exudation of fibrin, neutrophils, and macrophages, with necrosis of the bronchial epithelium, and formation of intra-vascular thrombi of adjacent blood vessels (thick arrow). **h** Activation of intra-alveolar and intra-bronchial macrophages (arrows). **i** Multifocal areas of caseous necrosis (asterisks) surrounded by a zone of inflammatory cells and encapsulated in thick fibrous tissue capsules. **j** Magnification of **i** showing that the zone of inflammatory cells (thin arrow) and fibrous tissue capsule (thick arrow) separate the necrotic area (asterisk) from the surrounding area. *Bar* = 200 μm for **a**, **c**, **d**, **e**, **f**, and **i**. *Bar* = 100 μm for **b**, **g**, **h**, and **j**

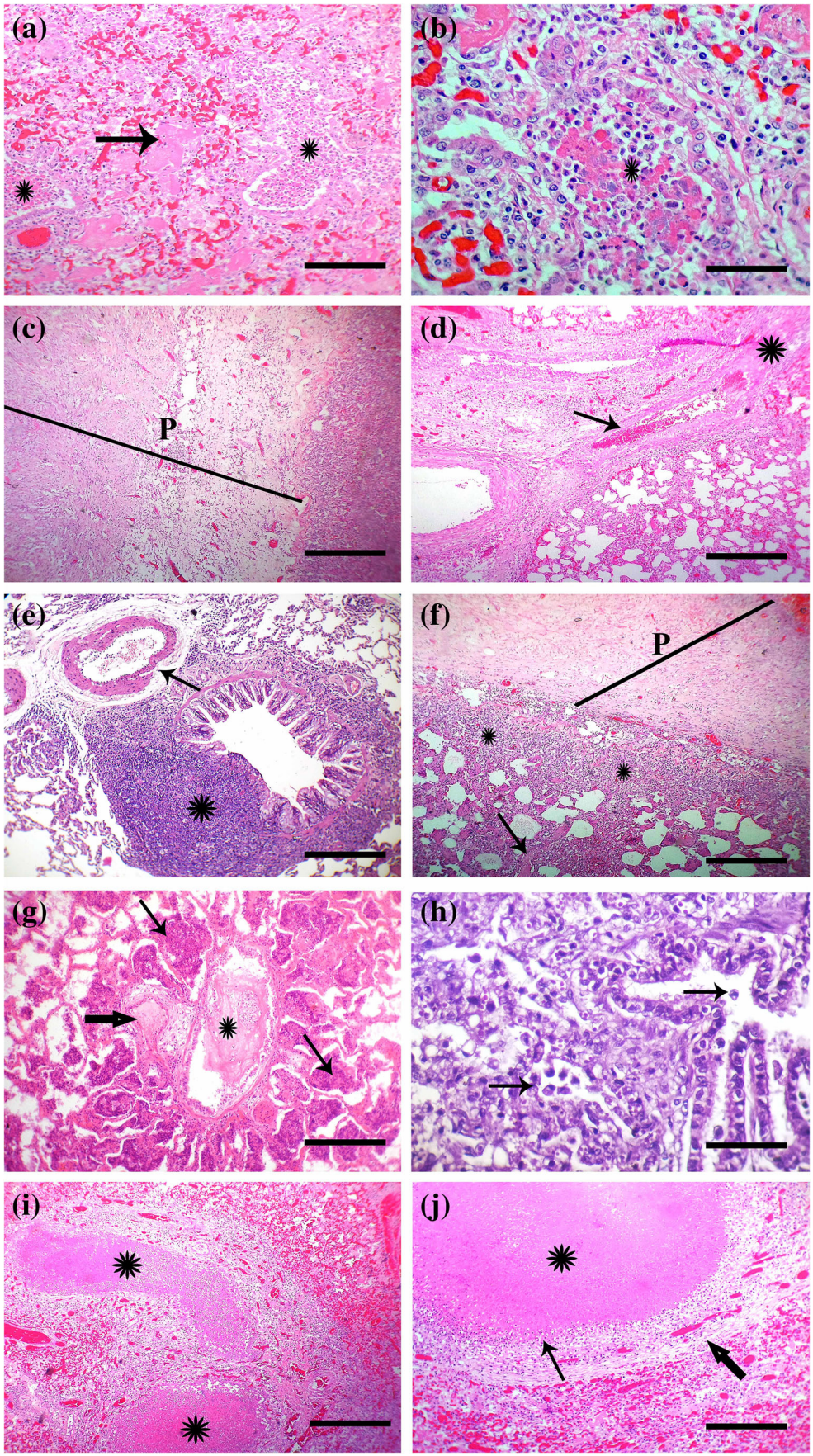
three different stages of disease were identified, namely, per-acute, acute, and chronic stages. Per-acute cases are characterized by sudden death and severe lung marbling. However, acute cases suffered fever, corneal opacity, and severe respiratory manifestations with lung marbling and exudative pleuritis. The chronic cases showed emaciation and mild respiratory signs, with characteristic sequestrum formation and adhesive pleuritis. These findings were completely consistent with the early obtained results by many investigators (MacOwan and Minette 1977; Thiaucourt and Bölske 1996; Wesonga et al. 1998; Nicholas 2002; Mondal et al. 2004; Rurangirwa and McGuire 2012).

Consistent with these results, histopathologic examination of lung tissue sections revealed fluctuations between the three different stages of fibrinous broncho- and pleuropneumonia, ranging from per-acute to acute or chronic stage of disease. In our study, the nature of the histopathologic lesions from CCPP-infected goats was consistent with that of the classic pulmonary lesions of CCPP mentioned by Thiaucourt and Bölske (1996) and Wesonga et al. (1998). Thrombosis of intra- and interlobular arteries and lymphatics was common in our study, giving rise to lung necrosis and infarction (Masiga et al. 1996; OIF 2000), while vasculitis could explain the marked exudation and pleurisy. This result was in complete agreement with almost all previous studies (FAO 1997; Gull et al. 2013; Francisco et al. 2015). The isolation of Mccp is considered a confirmatory diagnosis; in this study, the characteristic red colonies of mycoplasma were identified in all cultured samples. However, proper isolation and identification is a difficult task, in part due to the fragility of the colonies and the fastidious nature of the pathogen, and requires a high level of technical expertise (Bolske et al. 1996). Therefore, molecular tests are used regularly as highly specific and sensitive diagnostic tools for CCPP; these tests are beneficial and are considered to be accurate for identification and confirmation of the disease (Yatoo et al. 2019). Findings of the current study confirmed the culture positivity by group-specific PCR in 100% of the isolated colonies.

We evaluated whether early intervention resulted in a high cure rate and a decreased percentage of carriers and minimized the risk of antibiotic resistance; our findings confirmed that the marbofloxacin group and spiramycin group had a higher cure rate (70%) than the oxytetracycline group (40%) and a lower fatality rate (30%) than the oxytetracycline group (60%). Similarly, Ozdemir et al. (2006) reported that some types of antibiotics, including fluoroquinolones (such as danofloxacin), tetracyclines, and the macrolide family, can be effective in the early stage of infection. However, rare cases show complete elimination of mycoplasma. Moreover, animals could be potential carriers after recovery; the potential risk of the spread of *Mccp* infection from recovered animals remains to be elucidated.

Table 3 The mortality and cure rate of CCPP-infected animals treated with marbofloxacin, spiramycin, or oxytetracycline

Group	Cure rate		Died	
	No.	%	No.	%
Marbofloxacin group (10 animals)	7	70	3	30
Spiramycin group (10 animals)	7	70	3	30
Oxytetracycline (10 animals)	4	40	6	60


(a)
(b)
(c)
P
(d)
(e)
(f)
P
(g)
(h)
(i)
(j)

Conclusions, limitations, and future perspective

Based on the findings of this study, the occurrence, epidemiological status, case fatality, molecular identification, and pathologic features of CCPP in goats and sheep are considered novel for *Mccp* in Egypt in cities on the northern coastal road (El Hammam and Al Alamein); neighboring countries are also at risk. Therefore, a comprehensive survey should be conducted to determine whether there are other infected areas. Additionally, it can be concluded that treatment is effective only if given early. However, the relatively small number of examined animals and lack of investigation of the inherent resistance to CCPP in the treatment trial are important limitations of this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement The handling of animals used in the study was performed according to the accepted national and international guidelines for animal welfare.

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