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LETTER TO THE EDITOR

Methicilin-susceptible *Staphylococcus aureus* clonal complex 398: An unusual agent of necrotizing pneumonia

A 62-year-old female patient was admitted to the emergency department (ED) with a 7-day presentation of worsening cough, dyspnea, and pleuritic chest pain. She was unemployed and past medical history included a follicular lymphoma in remission and ischemic heart disease. She was vaccinated against SARS-CoV-2 and Influenza. Upon admission, the patient was hemodynamically stable, afebrile, tachypneic, with a peripheral oximetry of 93 % on oxygen via nasal cannula (1 L/min). Pulmonary auscultation of the right hemithorax was reduced. Arterial blood gas demonstrated adequate oxygenation and respiratory alkalosis. Laboratory evaluation revealed neutrophilic leukocytosis and high C-reactive protein. SARS-CoV-2 antigen and polymerase chain reaction were positive (cycle threshold [Ct] 29.4). Computerized tomography (CT) showed lung consolidation of the left superior and inferior lobes with a loculated pleural effusion (Fig. 1A). Empirical therapy with ceftriaxone and clarithromycin was started.

The patient deteriorated over 48 h with severe hypoxemic respiratory failure, requiring endotracheal intubation and ICU admission. Thoracocentesis revealed empyema that was drained with improvement of lung mechanics. Positive urinary antigen for *Streptococcus pneumoniae* motivated seven days of ceftriaxone and three days of clarithromycin. Microbiological testing showed MSSA on bronchoalveolar lavage (BAL) and tracheal aspirate, with a positive respiratory viral panel for rhinovirus. Complete microbiological workup is described in Table 1. On the seventh day of admission, thoracic CT showed signs of necrotizing pneumonia with no evidence of obliteration in the arterial supply, such as segmental thrombosis (Fig. 1B). The possibility of a PVL-producing MSSA strain was considered, and antimicrobial therapy was altered to linezolid. Bacterial phenotype and genotype were requested. The MSSA clonal lineage was determined based on the sequencing of an internal fragment of the spa gene. MSSA isolate was identified as belonging to spa type t1451, commonly associated with clonal complex CC398. It showed resistance to clindamycin, having a susceptible phenotype to other antibiotics ($n = 21$), including cefoxitin. The PVL gene was not detected, however the genes encoding β- and γ-hemolysin were. The chp and scn genes of the Immune Evasion Cluster (IEC) were found through PCR testing, suggesting an underlying association with the CC398 human clade. The patient was extubated after 10 days of invasive mechanical ventilation. Pulmonary lobectomy and decortication were deemed unnecessary upon improvement of lung consolidation and pleural effusion (Fig. 1C). The patient was transferred to an intermediate-care unit and antibiotics maintained for five weeks, despite the switch to flucloxacillin. She was subsequently transferred to the Pulmonology ward where she underwent rehabilitation and weaning from oxygen therapy for one month. After that she was discharged to a rehabilitation unit and return home after three months, autonomous, despite maintaining some tiredness, and without the need for supplemental oxygen.

This is the first case of severe necrotizing community-acquired pneumonia due to a non-PVL MSSA CC398 strain reported in Portugal. This documentation is important since this agent, belonging to the human clade, has been frequently associated with colonization.[1]

Although the patient might have initially presented with a community-acquired pneumococcal infection, the clinical course of necrotizing pneumonia was attributed to MSSA. *S. pneumoniae* was never isolated in cultures and urinary antigens can persist after acute infection. The positive results for rhinovirus and SARS-CoV-2 could have influenced the clinical severity of the case. The interactions between viral and bacterial infections have been widely studied. However, the simultaneous positivity of rhinovirus PCR on the respiratory panel does not implicate it as an acute infectious agent, but it is frequently identified alongside S.aureus. After infection clearance, respective viral loads decrease.[2] SARS-CoV-2 pneumonia may coexist or even trigger a bacterial pneumonia.[3] However, in the case of our patient, the role of SARS-CoV-2 in determining the clinical-radiological aspects is not relevant. She presented high Ct and the dominant clinical picture of unilateral pneumonia with empyema favor a bacterial agent.

Necrotizing pneumonia caused by MSSA CC398 was rarely reported in the past. The most common clinical presentations of invasive disease were osteomyelitis and bloodstream infections.[4] What might be considered an easily treatable MSSA strain can, in fact, be a more virulent agent with implications regarding antibiotic choices. In our case, linezolid was essential due to its favorable pharmacokinetic

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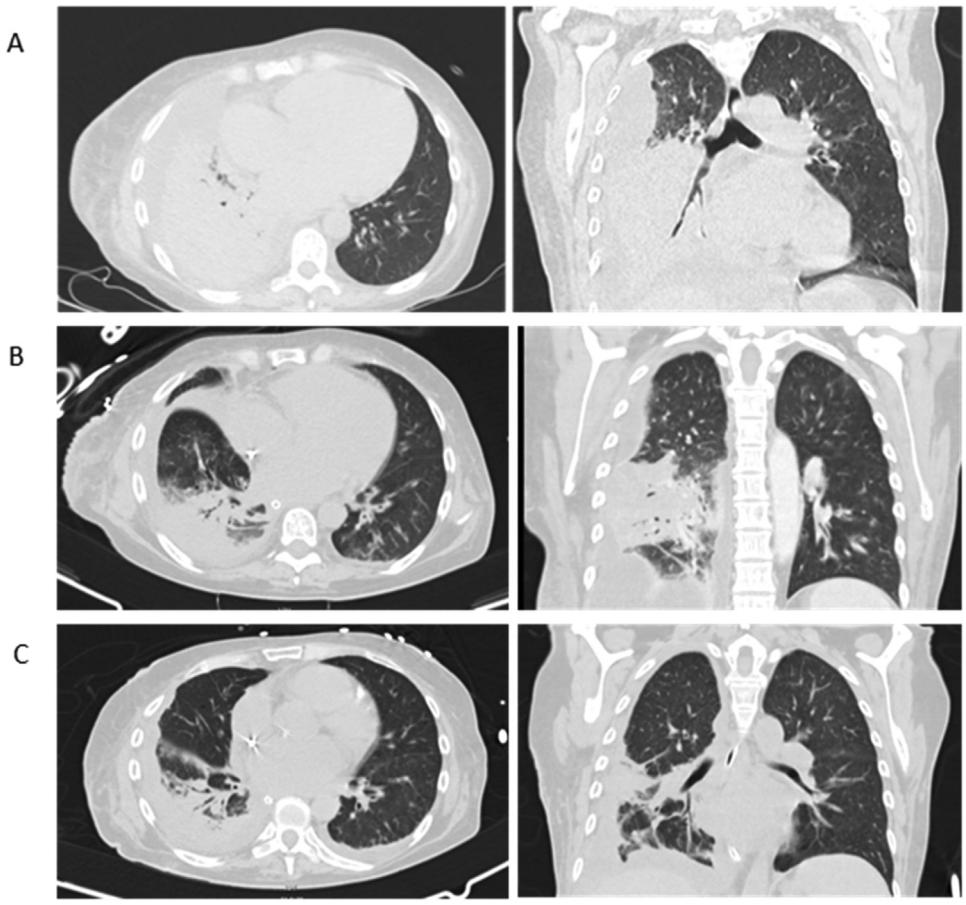

Fig. 1 A. Admission lung CT: extensive lung consolidation of the superior and inferior right lobes and large loculated pleural effusion; B. Day 7 lung CT (after chest drainage insertion):large heterogeneous lung consolidation with air bronchogram and gas-filled cavities predominantly in the apical and posterior basal segments of the lower right lobe; C. Day 22 lung CT (after chest drainage repositioning and removal): improvement of lung consolidation extension and pleural effusion, with 16 days of linezolid.

properties (better lung penetration). Although the MSSA strain was associated with a CC398 clone, the patient did not have a history of contact with either livestock or other animals. Furthermore, the isolate was PVL-negative and susceptible to tetracycline and methicillin, possessing genes typically carried within the IEC. This is in accordance with recent documentation of MSSA CC398 infections in young patients without previous animal contact.[5] The virulence mechanisms of CC398 MSSA human clade are unclear. Recent studies suggest that MSSA CC398 are becoming more resistant to antibiotics, more pathogenic to humans and have gained the ability to spread in the community and hospital settings.[6] This has been attributed to the acquisition of bacteriophages, leading to increased immune evasion and higher adhesion and invasion capacity of epithelial cells.[7] Different levels in the expression of α-toxin, phenol-soluble modulin and protein A, were also detected between ST398 and non-ST398 pneumonia isolates, possibly contributing to virulence [28]. It was shown that ST398 had an increased capacity to lyse human erythrocytes and neutrophils and cause severe multifocal necrotizing pneumonia,[7] as observed in this case. In cases of such clinical severity, we recommend the genotypic characterization, motivating further testing and active discussion with Microbiology Units to better classify underlying agents and strains that would otherwise persist unidentified.

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Table 1 Microbiological workup in ICU.

Microbiological Test	Specimen	Result	Timing of ICU stay (days)
Bacterial cultures	Tracheal aspirate	Negative	1
	Pleural effusion (exudate/empyema)	Negative	2
	Blood culture	Negative	2
	BAL	**MSSA**	4
	Tracheal aspirate	**MSSA**	4
	Blood culture	Negative	6
	CVC	Negative	6
	Arterial line	Negative	6
	Tracheal aspirate	Negative	9
	BAL	Negative	9
	Pleural effusion	Negative	9
	BAL (FB)[a]	Negative	15
Other Microbiological Tests			
Streptococcus pneumoniae antigen	Urine	**Positive**	1
Legionella pneumophila antigen	Urine	Negative	1
SARS-CoV-2 PCR	Nasopharyngeal swab	**Positive (high CT)***	1
SARS-CoV-2 antigen	Nasopharyngeal swab	**Positive**	1
MRSA PCR**	Nasal swab	Negative	1
Respiratory virus panel	Nasopharyngeal swab	**Positive:** **- Rhinovirus** **- SARS-CoV-2**	1
Ac Anti-HIV 1/2 e Ag P24 HIV 1 (chemiluminescence test)	Plasma	Negative	1
Mycobacterium stain (Ziehl Neelsen)	Pleural effusion	Negative	2
Galactomannan test	BAL***	Negative	4
Streptococcus pneumoniae antigen	BAL	Negative	4
Legionella spp. (culture)	BAL	Negative	4
Mycological culture	BAL	Negative	4
Mycobacterium stain (Ziehl Neelsen)	BAL	Negative	4
Mycobacterium culture	BAL	Negative	4
Mycological culture	Pleural effusion	Negative	9
Mycobacterium stain (Ziehl Neelsen)	Pleural effusion	Negative	9
Mycobacterium culture	Pleural effusion	Negative	9
HSV-1/HSV-2 PCR	Oral mucosa/vesicles	**Positive**/Negative	11
varicella-zoster virus PCR	Oral mucosa/vesicles	Negative	11
MRSA PCR	Nasal swab	Negative	29

[a]FB - Flexible bronchoscopy.
* cycle threshold.
** Polymerase chain reaction.
*** bronchoalveolar lavage.

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