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Pneumologia

COVID-19 complicated by multiple germs infection - case report and short literature review

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Abstract

English:

Introduction: *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is characterised by a varied clinical picture. In some cases the evolution may be unfavourable, progressing to pneumonia and acute respiratory distress syndrome.*
Clinical case: *A 70-years-old woman, with multiple comorbidities, was admitted for low-grade fever, dry cough and loss of appetite, symptoms that started 4 days prior to hospitalisation. She was initially diagnosed with mild coronavirus disease 2019 (COVID-19). On the 18th day of illness, there was an increase in inflammatory markers, progression of radiological lesions and SpO_2 dropped to 88% room air. Treatment with tocilizumab, remdesivir and high-flow oxygen therapy was initiated. Chest Computed tomography with pulmonary artery angiography ruled out suspected pulmonary embolism, but revealed a new pneumonic process and right pleural effusion, therefore antibiotic therapy was started. Imaging reassessment revealed excavation of the pneumonic process and persistence of pleural effusion. Reverse transcription polymerase chain reaction (RT-PCR) retesting for SARS-COV2 was negative and the patient was transferred to another hospital to undergo bronchoscopy and continue the treatment. Bacteriological examination of the induced sputum revealed the presence of Stenotrophomonas maltophilia, and in the bronchial aspirate was isolated Legionella pneumophilla; whereas the pharyngeal exudate highlighed the presence of Candida glabrata. Finally, the evolution was favorable. The patient was discharged with the recommendation to continue antibiotic therapy at home.*
Conclusions: *The evolution of SARS-CoV-2 infection may be unpredictable, the superinfection with other pathogens may influence the prognosis and progression of the disease.*

Keywords

COVID-19 pneumonia • superinfection • Legionella pneumophilla • Stenotrophomonas maltophilia

COVID-19 complicat cu infecție cu multipli germeni neobișnuiți – prezentare de caz clinic și scurt review

Rezumat

Romanian:

Introducere: *Infecția cu coronavirusul sindromului respirator acut sever 2 (SARS-CoV-2) se caracterizează printr-un tablou clinic variat. În unele cazuri evoluția poate fi nefavorabilă, progresând spre pneumonie și sindrom de detresă respiratorie acută.*
Caz clinic: *Prezentăm cazul unei paciente de 70 de ani, cu multiple comorbidități, care s-a prezentat pentru subfebrilitate, tuse seacă și inapetență, simptome care au debutat cu 4 zile înaintea spitalizarii. A fost diagnosticată inițial cu formă ușoară de COVID-19. În a 18-a zi de boală, s-a remarcat creșterea markerilor inflamatori, progresia leziunilor radiologice și scăderea SpO_2 la 88% în aerul atmosferic. S-a început tratamentul cu tocilizumab, remdesivir și oxigenoterapie cu flux mare. Tomografia computerizată cu angiografia arterelor pulmonare a exclus suspiciunea de embolie pulmonară, dar a evidențiat un nou proces pneumonic și revărsat pleural drept, motiv pentru care s-a început terapia cu antibiotice. Reevaluarea imagistică sugerează excavarea procesului pneumonic și persistența revărsatului pleural. Retestarea prin reacție în lanț a polimerazei în timp real (RT-PCR) pentru SARS-COV2 a fost negativă și pacienta a fost transferată la un alt spital pentru efectuarea bronhoscopiei și continuarea tratamentului. Examenul bacteriologic al sputei induse a evidențiat prezența Stenotrophomonas maltophilia, iar în aspiratul bronșic s-a izolat Legionella pneumophilla; exudatul faringian a evidențiat prezența Candida glabrata. În final, evoluția a fost favorabilă. Pacienta a fost externată cu recomandarea de a continua terapia cu antibiotice la domiciliu.*
Concluzii: *Evoluția infecției cu SARS-CoV-2 poate fi imprevizibilă, iar superinfecția cu alți agenți patogeni poate influența prognosticul și progresia bolii.*

Cuvinte-cheie

pneumonie COVID-19 • suprainfecție • Legionella pneumophilla • Stenotrophomonas maltophilia

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of the coronavirus associated with severe acute respiratory syndrome, the Betacoronaviridae family (1), a new virus that kept occupying the front page of medical journals since the end of December 2019 and produced an avalanche of events, with an unfavourable impact on the entire population. The disease caused by SARS-CoV-2 infection was named coronavirus disease (COVID-19). In March 2020, the number and severity of cases of SARS-CoV-2 infection exceeded expectations, that made World Health Organization (WHO) (2). On 26 December 2020, the number of deaths secondary to COVID-19 exceeded 78 million worldwide, according to the WHO (3). From our clinical experience, the evolution of COVID-19 is varied and unpredictable and can be marked by various complications (thrombosis, superinfections or coinfections, acute respiratory distress syndrome etc.).

Clinical case

A 70-year-old woman known to have multiple comorbidities (grade II hypertension therapeutically controlled, class II obesity, chronic kidney disease, polycystic kidney disease, total hysterectomy, appendicectomy), hospitalised on September 2020 at the Constanța Clinical Hospital of Infectious Diseases. At admission the patient reported low grade fever, dry cough and loss of appetite, started 4 days before. Her husband was recently confirmed with COVID-19. She was tested by reverse transcription polymerase chain reaction (RT-PCR) for SARS –COV2 with a positive result. Chest X-ray and computer tomography (CT) scan revealed interstitial pulmonary changes consistent with mild impairment (Figure 1), and laboratory data showed a slight increase in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) without leucopenia or lymphopenia (Figure 1). Antiviral therapy was administered according to the romanian national anti-SARS-COV2 infection guide [hydroxychloroquine, lopinavir / ritonavir] (4), associated with prophylactic anticoagulant, gastric protector and anti-inflammatory drugs. On the 10th day after the onset of the disease the patient became drowsy. The new blood samples showed a significant decrease in serum sodium levels, which required electrolyte rebalancing.

The evolution was initially favorable, until the 18th day of the disease, when symptoms of respiratory distress occured and SpO_2 dropped to 88% on room air, the level of inflammatory blood markers increased [serum Lactate Dehydrogenase (LDH) – 703 mg/dl, C-reactive protein – 225 mg/l, ESR – 60 mm/h, fibrinogen – 667 mg/dl] and radiological lung lesions progressed.

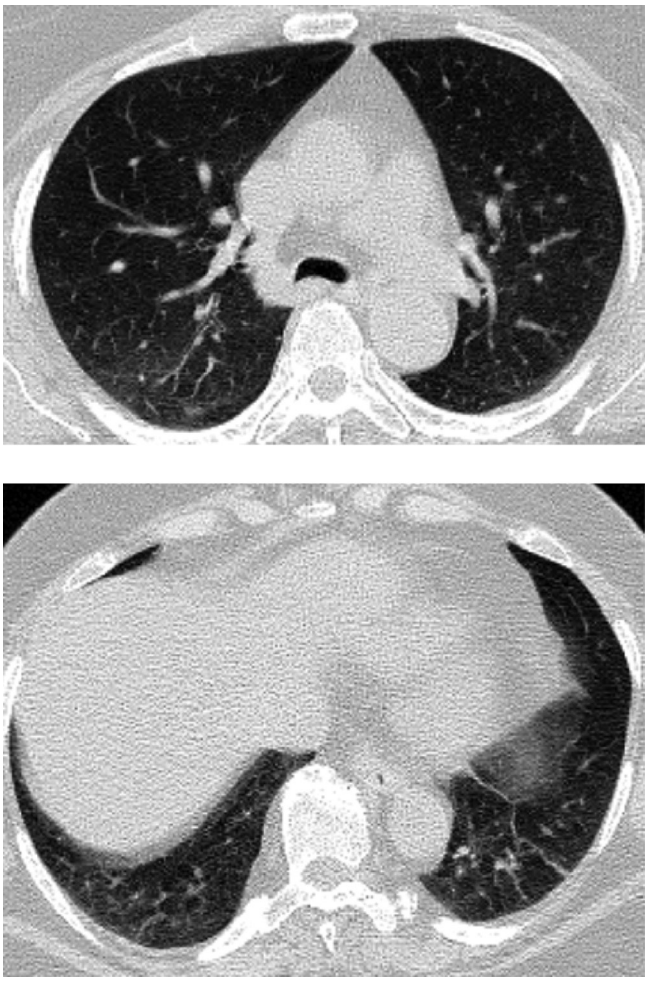


Figure 1. Chest CT images, day 13 from the onset of the disease – areas of pulmonary parenchyma with ground-glass appearance, with predominantly subpleural topography, disseminated panlobularly, predominantly at the level of the bilateral basal segments. These changes are associated with interlobular septal thickening and linear fibrotic tracts.

A new treatment plan was decided with tocilizumab, remdesivir, parenteral corticosteroid therapy, anticoagulant and high-flow oxygen therapy. High d-dimer values raised the suspicion of pulmonary embolism (PE) and a new CT scan with pulmonary artery angiography (CTPA) was performed (Figure 2).

The suspicion of PE was ruled out, but these investigations showed a new process in the right lower lobe, with air bronchogram and angiogram present, right pleural

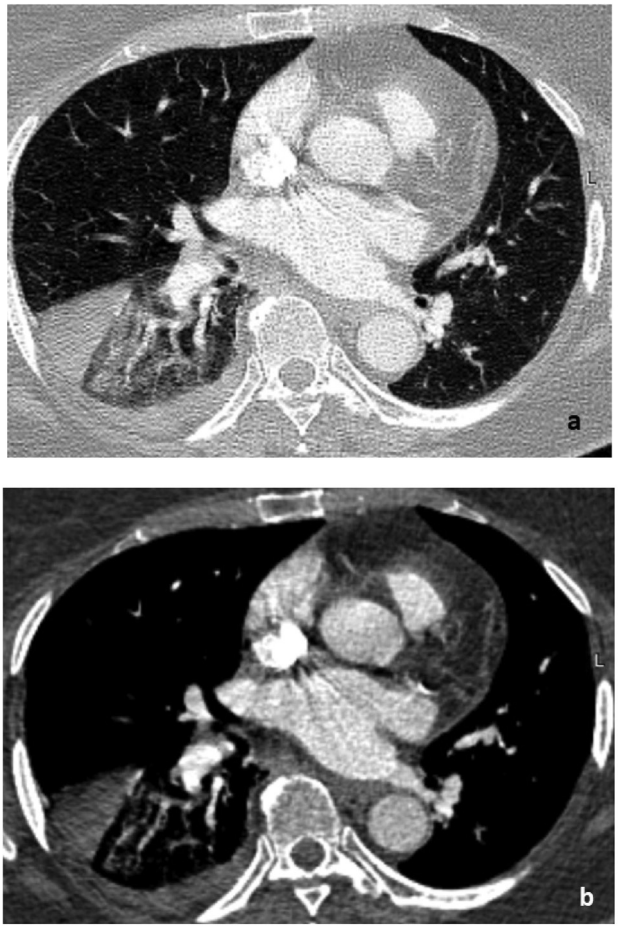


Figure 2. Chest computed tomography with pulmonary artery angiography (CTPA) (a) Axial nonenhanced CT image (lung window) shows a triangular condensation area (which occupies 40–50% of the right lower lobe), right pleural effusion and minimal progression of the ground-glass opacities specific to COVID19. (b) Axial contrast-enhanced CT image (mediastinal window) - homogeneously opacified pulmonary arteries, with angiogram at the level of the condensation process of the right lower lobe.

effusion. The ground-glass lung opacities specific to COVID-19 evolved from a score of 10 to a new score of 11 (compared to the previous examination). Given the patient's immunosuppression and in accordance with the Carmeli score (5), antibiotic therapy with meropenem, linezolid and trimethoprim/sulphamethoxazole was started.

Under treatment, the evolution was visibly favorable, evidenced by the correction of SpO_2 values, reduction of the biological inflammatory syndrome and procalcitonin levels (infectious process controled). As creatinekinase and D-dimer values remain elevated (Table 1), the cardiovascular surgeon's advice was to perform soft tissue and Doppler ultrasonography to rule out other possible sources of embolism in other vascular areas or haematomas that can cause fibrinolysis.

The patient had been experiencing a mild pain in her right thigh for several days, where a haematoma was detected by ultrasonography. The anticoagulant and antiplatelet therapy was stopped, the right lower limb was positioned at 30° and local application of ice and heparin treatment were carried out; re-evaluation would take place in the outpatient department after the cure of COVID-19 disease. Imaging reassessment suggests excavation of the pneumonic process and persistence of pleural effusion (Figure 3). The galactomannan test was negative. After retesting by RT-PCR for SARS-COV2 was negative, she was transferred to the Constanța County Emergency Hospital, to a non-COVID section, for further investigation and treatment.

Stenotrophomonas maltophilia was isolated after induced sputum, as the patient was already treated with trimetoprim/sulphametoxazole and the strain was susceptible to this combination. Bronchoscopy with sedation revealed a minimal diffuse bronchial appearance, hyperaemic bronchial mucosa, discreet oedema and reduced purulent secretions in the right lower lobe.

The sample of the bronchial aspirate was sent to Infectious Diseases Hospital Laboratory and by multiplex analysis (BIOFIRE-Pneumonia Panel plus-IVD) *Legionella pneumophila* was confirmed. The patient began to experience difficulty and pain when swallowing; so, pharyngeal exudate was collected, which confirmed the fungal infection with *Candida glabrata*. The final diagnosis was severe COVID-19 form, right lower lobe viral pneumonia complicated with bacterial and fungal superinfection. The clinical, paraclinical and radiological evolution was favourable under treatment (according to the antibiogram and fungigram). Chest X-ray performed before discharge showed dimensional reduction in the right lower lobe pneumonic process compared to the previous examination (Figure 4) and was discharged with the recommendation to continue the antibiotic therapy at home.

Discussions

In the study of Wu and McGoogan (6), most cases of COVID-19 were mild forms (81%) and did not require hospitalisation.

Severe forms of COVID-19 were manifested with viral pneumonia with respiratory distress syndrome (7). In their retrospective study, Zhou et al. (8) identified risk factors for death during hospitalisation, which are the advanced age, the increased value of d-dimers (>1 μg/mL) and the increased

Table 1. Patient laboratory data.

The day of the onset of the disease	ESR (mm/h)	Fibrinogen (mg/dL)	CRP (mg/L)	Serum LDH (U/L)	Procalcitonin (<0.5 – negative)	D-dimer (ng/mL)	CK (U/L)	Absolute Lymphocyte Count (cells x 10^9/L) and Percentage of Lymphocytes (%)
D 5	30	378	9	568			175	
D 8	25	281	3	520			227	
D 11	35	246	2	546	<0.5	469		
D 18	60	667	225	703			71	0.48 (2.1%)
D 19	100	738	343	643	0.69	1982		0.12 (0.4%)
D 20	80	754	229	633	0.62	2655	452	0.14 (0.7%)
D 21	80	674	146	693	0.45	3049	499	0.22 (1.4%)
D 23	70	476	52	856		2542	352	0.73 (6.3%)
D 25	10	423	27		0.06	2293		
D 28	15		3	725	<0.05	1594	726	

CRP, C-reactive protein; CK, creatine kinase; D, day; ESR, erythrocyte sedimentation rate; LDH, Lactate Dehydrogenase.



Figure 3. (a) Axial nonenhanced CT image (lung window) on day 22 of the onset of the disease - condensation process in the right lower lobe, right pleural effusion, areas of ground glass opacities, severity score of COVID-19 lesions = 11; (b) Axial nonenhanced CT image (lung window) on day 29 of the onset of the disease - the condensation process excavated and formed a cavity (30/22 mm diametre) and a wall with a thickness of approximately 13 mm; pleural effusion persists and the severity score of COVID-19 lesions = 9.

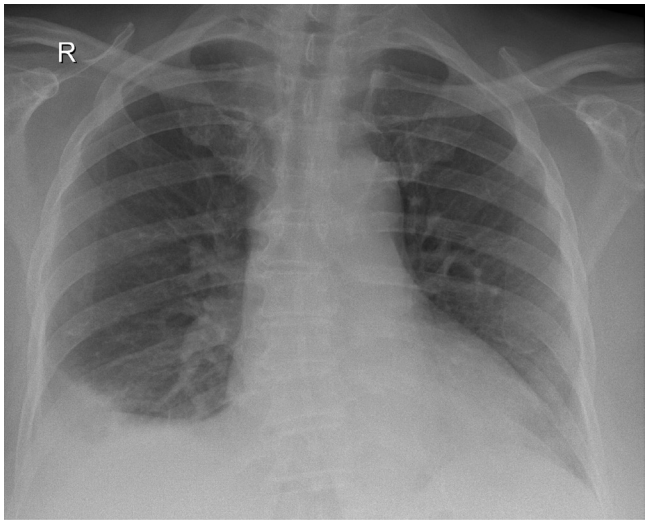


Figure 4. Pulmonary radiography at discharge.

SOFA score. There are limited and controversial data on coinfection in COVID-19. Garcia-Vidal et al. (9) in their retrospective study conclude that the rate of coinfection and superinfections in COVID-19 is low, but their presence causes severe forms of Covid-19 with a negative outcome. The most common pathogens responsible for co-infection were *Streptococcus pneumoniae* and *Staphylococcus aureus*, while superinfections were mainly caused by *Pseudomonas aeruginosa* and *Escherichia coli*. (9).

Xing et al. (10) in their double-center study on COVID-19 patients, the most common pathogens responsible for co-infection were Influenza A and Influenza B, but also *Mycoplasma pneumoniae* and *Legionella pneumophila*.

Instead, Chen et al. (11) identified *Acinetobacter baumannii*, *Klebsilla pneumoniae*, *Aspergillius flavus*, *Candida glabrata* and *Candida albicans* responsible for superinfections, in the COVID-19 confirmed cases.

Fu et al. (12) reported 5 cases of SARS-CoV-2 pneumonia complicated by secondary bacterial infection, the most common causes including *Burkholderia cepacia*, *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*. The presented studies have certain limitations due to the small number of patients in the studied cohorts.

The vast majority of co-infections or superinfections in COVID-19 cases have been described in critically ill patients who have previously received antibiotics and invasive mechanical ventilation (13). In our case the patient was in a severe condition and received antibiotics according to the guidelines, but was never under mechanical ventilation or non-invasive ventilation. An aspect that positively influenced the patient's evolution was the absence of resistance of antimicrobial genes to all identified germs.

Conclusion

This reported case of a old woman with multiple comorbiditis, diagnosed with severe SARS-COV-2 infection, with bacterial and fungal superinfection (*S. malthophilia*, *L. pneumophilla* and *Candida glabrata*), had a good evolution and prognosis based on an appropriate therapeutic management. Although the initial presentation was in the mild form of the disease, after day 18 of the onset of symptoms it rapidly evolved into a severe form with respiratory distress syndrome. The patient's prognosis was not favourable given the advanced age and associated pathologies, but the identification of multiple unusual pathogens helped us in the management of treatment.

It is important to consider superinfection with other pathogens in patients with severe forms of COVID-19, as they may influence the progression and prognosis of the disease, therefore, promptly diagnosing and appropriate therapeutic conduct are recommended.

Authors' contributions

IP and DET contributed to the conception and design of the case report. ED, IVS and RCC performed the literature review. IP wrote the first draft of the manuscript. DET, OCA and APF revised the manuscript. All authors have read and approved the final version of the manuscript.

Acknowledgements

Not applicable.

Conflict of Interest

The authors have no conflict of interest. The authors have obtained the ethical approvement for publishing the case.

References

1. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses; Gorbalenya AE, Baker SC. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology*. 2020;5(4): 536–544.
2. WHO Director-General's opening remarks at the media briefing on COVID-19: 11 March 2020. Published March 11, 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [Accessed 26th December 2020].
3. World Health Organization. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 [Accessed on 26 December 2020].
4. Ordinul nr. 1.418 din 7 august 2020 privind modificarea anexei la Ordinul Ministrului Sănătății, nr. 487/2020 pentru aprobarea protocolului de tratament al infecției cu virusul SARS-Cov-2. In: *Monitorul Oficial al României*. Partea I, nr. 242 din 24 martie 2020, Available from: http://legislatie.just.ro/Public/DetaliiDocument/229019 [Accessed 26th December 2020].
5. Slavcovici A, Streinu-Cercel A, Ţăţulescu D, Radulescu A, Mera S, Marcu C, et al. The role of risk factors 'carmeli score' and infective endocarditis classification in the assessment of appropriate empirical therapy. *Therapeutics, Pharmacology and Clinical Toxicology*. 2009;13(1): 52–56.
6. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13): 1239–1242.
7. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA*. 2020;323(16): 1574–1581.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229): 1054–1062.
9. Garcia-Vidal C, Sanjuan G, Moreno-Garcia E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clinical Microbiology and Infection*. 2021;27(1): 83–88.

10. Xing Q, Li GJ, Xing YH, Chen T, Li WJ, Ni W, et al. Precautions are needed for COVID-19 patients with coinfection of common respiratory pathogens. *medRxiv*.
11. Chen, Nanshan; Zhou, Min; Dong, Xuan; Qu, Jieming; Gong, Fengyun; Han, Yang; Qiu, Yang; Wang, Jingli; Liu, Ying; Wei, Yuan; Xia, Jia'an; Yu, Ting; Zhang, Xinxin; Zhang, Li (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, S0140673620302117–. https://doi.org/10.1016/S0140-6736(20)30211-7
12. Yiqi Fu, Qing Yang, Min Xu, Haishen Kong, Hongchao Chen, Yajie Fu, Yake Yao, Hua Zhou, Jianying Zhou, Secondary Bacterial Infections in Critical Ill Patients With Coronavirus Disease 2019, Open Forum Infectious Diseases, Volume 7, Issue 6, June 2020, ofaa220, https://doi.org/10.1093/ofid/ofaa220
13. Bassetti, M., Kollef, M.H. & Timsit, JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med 46, 2071–2074 (2020). https://doi.org/10.1007/s00134-020-06219-8