INTERNAL MEDICAL SCIENCES

Diagnosis and Treatment

Editor

Assoc.Prof. Dr. Onder Ozturk

The new edition of "Internal Medical Sciences: Diagnosis and Treatment" is scientific medical research in the internal medicine. This book is intended for experts, scientists and researchers who are just starting out in these areas of medicine. These are interdisciplinary and transdisciplinary areas from cardiology, pulmonary medicine, neurology, pediatri, infectious diseases, otorhinolaryngology and some other medical fields. In this book, scientists have presented contemporary topics and rare cases in the field of cardiology, pulmonary medicine, neurology, pediatri, infectious diseases, otorhinolaryngology

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Editor • Assoc. Prof. Dr. Onder Ozturk . 0000-0003-4204-0599

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website • http://www.livredelyon.com
e-mail • livredelyon@gmail.com

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PREFACE

The new edition of “Internal Medical Sciences: Diagnosis and Treatment” is scientific medical research in the internal medicine. This book is intended for experts, scientists and researchers who are just starting out in these areas of medicine. These are interdisciplinary and transdisciplinary areas from cardiology, pulmonary medicine, neurology, pediatri, infectious diseases, otorhinolaryngology and some other medical fields. In this book, scientists have presented contemporary topics and rare cases in the field of cardiology, pulmonary medicine, neurology, pediatri, infectious diseases, otorhinolaryngology. We hope that many medics will find useful and interesting content for their education and new research.

We are thanking to Livre de Lyon publishing house for supporting the publication of the book.

Assoc. Prof. Onder Ozturk , MD.
Editor

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CHAPTER I

VENTILATOR-ASSOCIATED PNEUMONIA (VAP) IN INTENSIVE CARE UNITS

Gulsen Iskender

(Dr.), Dr.Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, e-mail: golshan1669@hotmail.com

0000-0001-7619-1366

1. Introduction

Ventilator-associated pneumonia (VAP) continues to be important causes of morbidity and mortality in intensive care units despite advances in prevention, antimicrobial therapy and supportive care. It accounts for about half of hospital-acquired pneumonias (HAP) and estimated to occur in 9–27% of all mechanically ventilated patients (1). According to the 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines; VAP is a clinical diagnosis made in a patient who has been mechanically ventilated for ≥48 hours who develops a new or progressive lung infiltrate on imaging with clinical evidence of infection (eg, fever, purulent sputum, leukocytosis, and decline in oxygenation), together with a positive pathogen identified on microbiologic respiratory sample.VAP has been associated with long hospital stays, long duration of mechanical ventilation and significant costs (2).

2. Pathogenesis

The pathogenesis of VAP is related to the number and virulence of microorganisms entering the lower respiratory tract and the mechanical, humoral and cellular defense of the host. The primary route of infection is aspiration/microaspiration of organisms that have colonized the oropharyngeal or gastrointestinal tract. Aspiration can accure in healthy persons during sleep and in high proportion of severely ill patients. The presence of an endotracheal tube facilitates this event (3). Up to 75% of seriously ill patients will be colonized with microorganisms taken from the hospital environment within 48 hours of hospital admission mainly via the contaminated respiratory devices, water reservoirs and hands of hospital staff. Less frequently pneumonia may also develop as a result of bacteremia originating from a distant focus in intubated patients (4).

3. Clinical Presentation

There is no universally accepted, gold standard diagnostic criterion for VAP. Daily bedside assessment together with chest radiography gives clues about the presence of VAP. Fever, tachypnea, increased, purulent respiratory secretions, hemoptysis, rhonchi, decreased breath sounds, bronchospasm, decreased tidal volume and increased inspiratory pressure develop. In laboratory tests hypoxemia and lukocytosis can be detected with new or progressive infiltrates on chest radiograph or computed tomography (CT) (1). However none of these findings alone are indicative of VAP.

4. Diagnosis

The clinical diagnosis of VAP is difficult because the clinical findings are nonspecific. IDSA and ATS recommend a clinical diagnosis based upon a new lung infiltrate plus clinical findings that shows the infiltrat is of infectious origin which as mentioned above includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation (2). The chest radiograph can help to determine the severity of the disease (multilobar versus unilobar infiltrate) and identify complications such as pleural effusions or cavitation. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever >38ºC, leukocytosis or leukopenia, and purulent secretions) has a 69% sensitivity and 75% specificity for VAP (5). Chest CT, without contrast, is not routine in patients with suspected VAP but may be useful in symptomatic patients with a normal chest radiograph. It also helps in the follow-up of pulmonary infiltrates.

The diagnosis is confirmed when lower respiratory tract sampling identifies a pathogen. It has been shown that in bacterial diagnosis quantitative endotracheal aspirate cultures had a sensitivity of 48% and positive predictive value of 81%; quantitative bronchoalveolar lavage cultures had a sensitivity of 75% and positive predictive value of 77%. Respiratory samples should ideally be taken before starting antibiotic therapy or before making an antibiotic change because antibiotic therapy reduces the sensitivity of both microscopic analysis and culture. Peripheral blood cultures should be sent concomitantly (6). In 2017 guidelines published by the European Respiratory Society (ERS) / European Society of Intensive Care Medicine (ESCIM) / European Society of Clinical Microbiology / Infectious Diseases (ESCMID) / Asociación Latinoamericana del Tórax (ALAT), invasive sampling methods (eg. mini preferred bronchoalveolar lavage [BAL], bronchoscopic BAL or protected sample brush (PSB]) and quantitative cultures were recommended to be preferred for respiratory sampling (7). On the other hand the IDSA and

ATS recommendations are in line with noninvasive sampling with semiquantitative cultures for the diagnosis of VAP (2,6).

All respiratory tract samples should be sent for microscopic analysis (Gram stain) and cultures (preferably quantitative cultures). Microscopic analysis can be helpful in determining potential causative pathogen much earlier than the culture results (8). Quantitative cultures are not routinely performed in most laboratories. They are generally considered more labor-intensive and more costly than qualitative or semiquantitative cultures. In quantitative cultures typical thresholds for bacterial growth for endotracheal aspirates are; ≥1,000,000 colony forming units (cfu)/mL, bronchoscopic or mini-BAL ≥ 10,000 cfu/mL and for PSB ≥ 1000 cfu/mL. Noninvasive sampling (eg, endotracheal aspirates) with semiquantitative (or qualitative) cultures are the alternative approach preferred by IDSA and ATS because of the lack of clear evidence demonstrating superior outcomes (mortality or length of stay in hospital) with invasive sampling and quantitative cultures (described above) (2,6). However, it may be less accurate for sampling the alveolar component of the lower respiratory tract and lead to the over diagnosis of VAP. It may also be less suitable for patients with invasive pneumonia who are immunocompromised. Semiquantitative cultures are typically reported as heavy, moderate, low or no bacterial growth. Most experts consider moderate or heavy growth to be positive. Colonization is difficult to distinguish from infection with this method. So false-positive results are more likely, which can lead to over treatment of VAP. Qualitative cultures do not specify the amount of bacterial growth. VAP is considered to be present when a sample is positive and is less reliable than other methods.

Lung biopsy is not routinely performed in patients with suspected VAP. It may be reserved for patients in whom infiltrates are progressive under antibiotic treatment or if there is a suspicion of fastidious, difficult to growth microorganisms (eg, fungus, viruses) or non-infectious etiology (eg, cancer, cryptogenic organizing pneumonitis, vasculitis).

Molecular diagnostic tests can be used for more rapid identification of respiratory pathogens in VAP. Identification of resistance patterns (eg, methicillin resistance for *S. aureus*, carbapenemase presence for *Enterobacteriaceae*), by mulecular diagnostic tests offer the chance for rapid initiation of appropriate antibiotics (9). However these methods are not routinely performed and may be difficult to interpret. Polymerase chain reaction (PCR) is a fast and inexpensive technique that amplifies small segments of microbial DNA for identification. Multiplex PCR tests allow multiple pathogens to be investigated at the same time and assist in the diagnosis and appropiate antibiotic management of critically ill patients for whom the list of potential pathogens may be wide (10).

The entities of ventilator-associated conditions (VAC) and infection-related ventilator-associated complications (IVACs), which were introduced by the United States Centers for Disease Control and Prevention (CDC) for the purposes of surveillance and quality improvement, do not aid diagnosis and treatment decisions for individual patients.

5. Microbiology

A wide variety of microorganisms including aerobic gram-negative bacilli (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Pseudomonas aeruginosa*, *Acinetobacter* spp) and gram-positive cocci (eg, *Staphylococcus aureus*, including methicillin-resistant *S. aureus* [MRSA], *Streptococcus* spp) and viruses can cause VAP. Sometimes these infections are polymicrobial. In immunocompromised hosts a substantial fraction of these pneumonias may be due to fungal agents (11,12). According to the National Health Related Infections Surveillance Network (UHIESA) 2019, in Turkey the distribution of pathogens associated with VAP are as follows; gram-positive cocci 4,5% (S. aureus: 3,4%), enterobacteriacea 29,8% (Klebsiella spp 19.5%), non fermentative gram negative bacilli 63,5% (Acinetobacter spp: 40,6%, P. aeruginosa: 18,6%) and fungal agents 0,5% (Candida spp: 0,4%) (13). We evaluated mini-BAL and concomitant blood culture results in VAP cases in Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital during January 1, 2018 - December 31, 2019. The distribution of microorganisms isolated is shown in table 1. As seen in the table, *Acinetobacter baumanii* constitutes the majority of isolates (84.9%). Although there are differences according to the microorganisms that grow, simultaneous blood culture positivity has been detected in 17-100% of the cases.

Table 1: Microorganisms isolated from mini-BAL samples in VAP cases

(Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital)

Microorganisms	BAL/mini BAL N(%)	Concomitant bacteremia N(%)
Acinetobacter baumanii	45 (84.9)	6 (13.3)
Klebsiella pneumonia	4 (7.5)	1 (25)
Pseudomonas aeruginosa	3 (5.7)	1 (33.3)
Serratia marcencens	1 (1.9)	1 (100)
Total	53 (100)	9 (17)

The prevalence of certain pathogens (eg, anaerobes) may be underestimated because of special culturing techniques are required to identify them. Anaerobes may play a relatively minor role in the pathogenesis of VAP due to the successful treatment of VAP by regimens that do not include anaerobic coverage. Differences in host factors and hospital flora also influence the patterns of pathogens.

The role of multi drug resistant (MDR) pathogens has been increasing in VAP etiology in recent years. CDC and the European Centre for Disease Prevention and Control (ECDC) have developed standard terminology for antimicrobial-resistant gram-negative bacilli, which are important causes of HAP and VAP (14).

●MDR refers to acquired nonsusceptibility to at least one agent in three different antimicrobial classes.

●Extensively drug resistant (XDR) refers to nonsusceptibility to at least one agent in all but two antimicrobial classes.

●Pandrug resistant (PDR) refers to nonsusceptibility to all antimicrobial agents that can be used for treatment.

Prolonged hospitalization and recent exposure to antibiotics are two of the most important risk factors for MDR pathogens. Awareness of the

susceptibility patterns of nosocomial pathogens in hospitals is important in choosing the appropriate empirical antimicrobial therapy. Risk factors for MDR VAP are summarized in table 2.

Table 2: Risk factors for multidrug-resistant ventilator-associated pneumonia

Risk factors for MDR pathogens:
▪ IV antibiotic use within the previous 90 days ▪ Septic shock at the time of VAP ▪ ARDS preceding VAP ▪ ≥ 5 days of hospitalization prior to the occurrence of VAP ▪ Acute renal replacement therapy prior to VAP onset
▪ **Risk factors for MDR *Pseudomonas* and other gram-negative bacilli:** ▪ Treatment in an ICU in which >10 percent of gram-negative isolates are resistant to an agent being considered for monotherapy ▪ Treatment in an ICU in which local antimicrobial susceptibility rates are not known ▪ Colonization with OR prior isolation of MDR *Pseudomonas* or other gram-negative bacilli
▪ **Risk factors for MRSA:** ▪ Treatment in a unit in which >10 to 20 percent of *Staphylococcus aureus* isolates are methicillin resistant ▪ Treatment in a unit in which the prevalence of MRSA is not known ▪ Colonization with OR prior isolation of MRSA

MDR: multidrug resistant; IV: intravenous; VAP: ventilator-associated pneumonia; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; MRSA: methicillin-resistant *S. aureus*. *Adapted from: Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016; 63:e61.*

Antimicrobial susseptibility pattern of VAP cases in our hospital (Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital during January 1, 2018 - December 31, 2019) is shown in table 3. As seen in the table, *Acinetobacter baumanii*, the most frequently isolated

microorganism, were found as MDR and there is high antimicrobial resistance rate in *Klebsiella pneumonia* as the second most common isolate.

Table 3: Antimicrobial resistance pattern of microorganisms isolated from mini-BAL samples in VAP cases

(Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital)

Microorganisms	3rd.G ceph[a]	4th.G ceph[b]	Carb[c]	AG	Colistin	Tig[e]	Cef-sulb[f]	Pip-taz	Lev[h]	TMP-SMX[i]
Acinetobacter baumanii N:45 (84.9%)	45 100%	45 100%	45 100%	40 88.8%	1 2.2%	13 28.8%	43 95.5%	45 100%	45 100%	45 100%
Klebsiella pneumonia N:4 (7.5%)	3 75%	3 75%	2 50%	1 25%	1 25%	1 25%	2 50%	3 75%	3 75%	2 50%
Pseudomonas aeruginosa N:3 (5.7%)	1 33.3%	1 33.3%	1 33.3%	0 0.0%	0 0.00%	1 33.3%	0 0.00%	1 33.3%	1 33.3%	1 33.3%
Serratia marcencens N:1 (1.9%)	1 100%	0 0.0%	0 0.0%	0 0.0%	1 100%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%
Total N: 53 (100%)	50 94.3%	49 92.4%	48 90.5%	41 77.3%	3 5.6%	15 28.3%	45 84.9%	49 92.4%	49 92.4%	48 90.5%

[a]:third generation cephalosporin, [b]: 4th generation cephalosporin, [c]:carbapenems, [d]: aminoglycosides, [e]: tygecycline, [f]: cefoperazone sulbactam, [g]: piperacillin tazobactam, [h]: levofloxacin, [i]:trimethoprim-sulfamethoxazole

6. Additional Diagnostic Tests

Biomarkers including procalcitonin, C-reactive protein (CRP), and soluble triggering receptor (sTREM-1) in BAL fluid and the clinical pulmonary infection score (CPIS), are additional diagnostic tests that have little role in the evaluation of suspected VAP (2). Procalcitonin may be useful in patients with confirmed VAP for making the decision to discontinue antibiotic therapy and it may be a useful prognostic marker (15,16). The CPIS combines clinical, radiographic, physiologic, and microbiologic data into a numerical result (table 4). At first a score of CPIS greater than 6 was thought to be related to VAP, but studies show that CPIS identified VAP with a sensitivity and specificity of only 60% and 59%, respectively (17).

Table 4: Clinical Pulmonary Infection Score

Body temperature ≥ 36.5 or ≤ 38.4 = 0 point ≥ 38.5 or ≤ 38.9 = 1 point ≥ 39 or < 36.5 = 2 point	**Pulmonary infiltration in chest X-ray** No infiltration = 0 point Diffuse infiltration = 1 point Localized infiltration = 1 points
Leukocyte count, microscopy ≥ 4000 or ≤ 11.000 = 0 point < 4000 or > 11.000 = 1 point Rod form ≥ % 50 = Add 1 point	**Progression in pulmonary infiltration** Radiographic progression (-) = 0 point Radyografic progression (+) (After the exclusion of HF and ARDS) = 2 points
Tracheal secretion Tracheal secretion (-) = 0 point Tracheal secretion with less purulence = 1 point Abundant purulent secretion = 2 points	**Pathogenic bacteria in tracheal aspirate culture** No or few pathogenic bacteria = 0 point Moderate or high levels of pathogenic bacteria = 1 point Pathogenic bacteria to be seen in Gram staining, add 1 point
Oxygenization PaO_2/FiO_2, mmHg > 240 or ARDS (ARDS: PaO_2/FiO_2 < 200, PaO_2/FiO_2 < 200, PAWP ≤ 18 mmHg and bilateral acute infiltration) = 0 point PaO_2/FiO_2, mmHg ≤ 240 or ARDS = 2 points	Total (>6 is accepted as pneumonia) ARDS: acute respiratory distress syndrome; HF: heart failure; PAWP: pulmonary artery wedge pressure

7. Prevention

Basic practices that were recommended by Society for Healthcare Epidemiology of America (SHEA) / IDSA for preventing VAP in all acute care hospitals include (18):

- Avoiding intubation when possible (eg, noninvasive ventilation)
- Minimizing transport while ventilated (when feasible)
- Implementation of weaning protocols
- Minimizing sedation
- Maintaining and improving physical conditioning
- Minimizing pooling of secretions above the endotracheal tube cuff
- Elevating the head of the bed and
- Maintaining ventilator circuits

In addition, proper hand hygiene, protective gloves and clothing of health staff, prevention of gastric distension, continuous active, prospective nosocomial infection surveillance are important in reducing nosocomial infections and VAP. Combining a set of key prevention measures into one bundle is a practical way to improve care and reducing the incidence of VAP among patients at risk. Typical bundle components include educational programs, technical measures, surveillance, and feedback. However, there is no consensus on what maintenance measures should be included in the bundles.

8. Treatment

Once VAP is suspected clinically, empiric antimicrobial therapy should be started as soon as possible specially in patients with signs of septic shock or rapidly progressive organ dysfunction (2)

Empiric therapy for VAP should include agents with activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli and should be based upon knowledge of the pathogens' susceptibility patterns within the health care setting as well as the patient's risk factors for multidrug resistance, including their prior microbiology data. Gram stain of respiratory secritions can help for guiding the choice of initial therapy. The appropriate approach would be early and aggressive antimicrobial initiation in patients with symptoms of sepsis or septic shock, and early de-escalation according to the causative pathogen and susceptibility pattern or when an alternative diagnosis is made. Empiric treatment choices should be based on the local distribution of pathogens causing VAP and their antimicrobial susceptibility patterns (19). Antimicrobial selection should also be based upon risk factors for MDR pathogens (table 2). For patients with risk factors for MDR pathogens, empiric broad-spectrum multidrug therapy is recommended. Potential drug toxicity and interactions, cost, availability, and clinician familiarity with the medications also should be considered. Antibiotic therapy should be narrowed/tailored based on microbiological results and susceptibility pattern of responsible microorganisms.

IDSA recommendations on initial treatment of VAP is summarized in table 5 (2).

Table 5: IDSA recommendations on initial treatment of VAP

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Drug levels and adjustment of doses and/or intervals required.

[b] Extended infusions may be appropriate. Please see section XIII on pharmacokinetic/pharmacodynamic optimization of antibiotic therapy.

[c] On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality.

[d] The dose may need to be lowered in patients weighing <70 kg to prevent seizures.

[e] Polymyxins should be reserved for settings where there is a high prevalence of multidrug resistance and local expertise in using this medication. Dosing is based on colistin-base activity (CBA); for example, One million IU of colistin is equivalent to about 30 mg of CBA, which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg = 10 000 units) [136].

[f] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

9. Conclusion

VAP occurs frequently in intensive care units and is one of the major causes of morbidity and mortality specially in critically ill patients. The first step in VAP management should be the preventive measures that can be directed by bundle applications created in line with the advice of international guidelines. The second important step is early diagnosis of VAP by continuous monitoring of patients' clinical condition, laboratory and imaging findings. Taking necessary culture samples and early initiation of appropriate empirical antimicrobial therapy based on hospital surveillance data are the next steps. Antimicrobial de-escalation according to the microbiological culture results and the clinical response of the patient is an important issue that plays an important role in preventing unnecessary and inappropriate use of antibiotics and the development of antibiotic resistance.

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CHAPTER II

THE DIAGNOSIS AND TREATMENT OF LUNG ABSCESS IN VIEW OF CURRENT RESEARCH

Aydın Kant

(Dr.), Trabzon Vakfikebir State hospital, Trabzon, Turkey, e-mail: aydinkant@yahoo.com

0000-0003-2914-2478

1.Introduction

Lung abscess is a cavitary lesion characterized by necrosis of the lung tissue caused by pyogenic microorganisms and is defined as a local suppurative process within the lung (1). This disease can be classified by its duration, etiology and passage of transmission. Lung abscess can be divided into two groups as acute (less than 6 weeks) and chronic (more than 6 weeks) (1). Etiologically, lung abscesses can be labelled as primary and secondary (1, 2). Primary lung abscess occurs in patients prone to aspiration or otherwise healthy individuals, with no underlying lung lesions. Secondary lung abscess develops in the presence of underlying lung lesions or on the basis of a systemic disease such as extrapulmonary infection, sepsis, immunosuppression or malignancy (1, 2). Considering the route of spread, the disease is grouped as bronchogenic (aspiration of oropharyngeal secretions, bronchial obstruction by the tumor, foreign body, enlarged lymph nodes, congenital malformation) and hematogenic (abdominal sepsis, infective endocarditis, septic thromboembolism) lung abscesses (1).

2.History

The clinical symptoms and treatment of lung abscess were first described by Hippocrates (1). In the pre-antibiotic period, one third of patients with lung abscess died, one third recovered completely, and the rest survived with sequelae such as chronic lung abscess, pleural empyema, or bronchiectasis (1, 3). While the mortality rate of lung abscess was quite high in the past centuries, this rate decreased significantly with open drainage and antibiotic treatment (4,5). Similarly, improvements in oral and dental hygiene have reduced the incidence of lung abscess (1).

3.Pathogenesis

Although abscess may occur in the lung due to reasons such as direct inoculation due to inhalation and trauma, contamination from the

diaphragm or mediastinum, and hematogenous transmission, the most important risk factor is the aspiration of the material in the oropharynx. In cases that cause confusion, sedative drug and alcohol use, epilepsy, head trauma, cerebrovascular diseases, diabetic coma and other diseases that disrupt the general condition, suppression of the gag reflex also facilitates the aspiration of the oropharyngeal flora and constitutes an important risk factor group. Aspiration during dental and periodental sepsis also facilitates abscess formation. Adhesions in the esophagus that cause swallowing disorders and gastroesophageal reflux can facilitate aspiration. On the other hand, bronchial obstructions caused by malignancy, inflammation and foreign bodies in the lung can contribute to abscess formation by preventing the clearance of the aspirated oropharynx material (6). Conditions that suppress the functions of the respiratory system defense mechanics, smoking and pre-existing diseases that impair the natural immunity of the organism; factors such as viral infections, chronic liver and kidney disease, diabetes, corticosteroid, intravenous drug use and sepsis are other factors that facilitate abscess formation in the lung (7). Pulmonary abscess may occur with the initiation of suppurative infection in the lung parenchyma distal to the narrowing or obstruction of the bronchi for any reason. This situation is more common in tumors with bronchial obstruction and foreign body inhalation (8). Pneumonia foci may also become abscessed. Especially, necrotizing pneumonia caused by *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus* spp and *Pseudomonas aeruginosa* abscesses more frequently than other pneumonias (6-8). In the focus of consolidation, first small multiple abscesses and then large abscesses are formed by their combination. Staphylococcal abscesses are often complicated by empyema and pyo-pneumothorax (9). Septic embolism caused by an infection in the extra pulmonary focus can form lung abscesses by occluding the pulmonary artery branches. Such abscesses can be seen in staphylococcal infections such as osteomyelitis, furuncle, abdominal and pelvic sepsis, infective endocarditis, use of infected intravenous cannula, and septic thrombophlebitis. Hematogenous lung abscesses are usually multiple and localized in the peripheral parts of the lung (9, 10). Since the drainage bronchi of these foci are small, cellular infiltration and edema caused by inflammation cause blood pressure cysts, rupture into the pleura and empyema by obstructing the bronchi (10). Also, bronchogenic cysts can become infected, leading to lung abscess. Cystic lesions such as bulbs and blebs are rarely infected since they do not contain secretions (10). Infection of pulmonary hydatid cysts after perforation gives typical clinical findings of lung abscess. After the perforated hydatid cyst is completely excreted, the remaining cavity may become infected secondarily and shows a course like an infected lung abscess. If the cyst cannot be removed completely, it becomes infected easily and frequently as a result of the foreign body

reaction caused by the particles remaining inside, and gives symptoms and signs such as chronic lung abscess (6, 8). Abscesses in the upper part of the liver can penetrate the diaphragm and open into the lungs. As a result of perifocal reactions occurring in the diaphragmatic pleura, adhesion occurs between the upper face of the diaphragm and the lower face of the lung in the lesion area, thus lung abscess develops directly without empyema in the pleura. Sweep appendicitis and sweep cholecystitis cause lung abscess in this way. Rarely, perinephritic abscesses and sometimes together with nephrobronchial fistulas can lead to lung abscess. In addition, infections in the esophagus, mediastinum and vertebrae can spread to the lungs and cause abscesses, even if they are rare. Although tracheoesophageal fistula is a rare congenital formation, it can cause bronchiectasis and abscess formation in children. Amoebas should be considered in the etiology of abscesses in the lower right lung of patients with chocolate-colored sputum (11). The aspiration of mouth and throat flora to the lungs during general anesthesia and the difficulty in removing the aspirated septic material and bronchial secretion due to the ineffectiveness of cough in the post-operative period may cause abscess formation. In septic surgeries, bacteria-laden emboli from the operation site spread to the lung by hematogenous route and cause suppuration (9). Pulmonary abscess may occur as a result of the implantation of the infectious material into the lung, in injuries caused by firearms and piercing weapons, in traumatic events that cause the broken rib ends to stick into the lung. Infection of a traumatic hematoma may also cause abscess (9).

4.Pathology

Lung abscesses usually begin as small necrotic foci or microabsities in a consolidated lung area. It can occur in any part of the lung, single or multiple. Abscess formation is mentioned when these suppurative microabse foci combine to grow and reach 1-2 cm in diameter. If this pathological process is prevented by early antimicrobial treatment, recovery is achieved without any damage. However, if the treatment cannot be done or is not sufficient, the inflammation becomes chronic and continues. If the abscess is fistulized by eroding the neighboring bronchus, the purulent content of the abscess spreads to the bronchus and malodorous sputum expectoration begins (12, 13). Aspiration-induced pulmonary abscesses are more common in the right lung and are usually single, as the right main bronchus is more vertical (14). Abscesses that develop during the course of pneumonia or bronchiectasis are usually multiple, basal and diffuse distributed. Septic embolus and pyemic abscesses are numerous due to their irregular and random development and may involve any part of the lung (13). If a connection occurs between the abscess cavity and an airway, the exudate in the abscess is partially drained and a cavity

containing air forms. Added saprophytic infections tend to proliferate among the necrotic debris accumulated in the abscess cavity. In this way, continuous infection creates large multilocular cavities with bad odor, green-black color, with poorly defined edges, called lung gangrene. Cardinal histological change in all abscesses is suppurative destruction of the lung parenchyma within the central cavitation area. In chronic cases, abundant fibroblastic proliferation creates a fibrous wall (12-14).

5.Diagnosis

Patients typically show signs of upper respiratory tract infection. Early signs and symptoms of lung abscess are indistinguishable from pneumonia and include chills, cough, night sweats, dyspnea, weight loss and fatigue, chest pain, and sometimes fever with anemia (15). Hemoptysis is an indication of the evacuation of the necrotic contents of the abscess cavity. This first symptom is usually followed by the production of purulent, sometimes foul-smelling sputum in abscesses due to anaerobes. Abundant sputum production in the form of vomiting can be observed with the opening of the abscess to the bronchus. Staphylococcus aureus, gram-negative bacilli, and amoeba abscesses can show a rapid and severe course (16). In the late stage, amphoric or cavernous breathing, signs of pleurisy, and large abscesses are dull. Breathing sounds are attenuated. Clubbing may develop in chronic abscesses (1, 6). In the early stages of the disease there is leukocytosis and the erythrocyte sedimentation rate is increased. Hypochromic anemia can be seen with the toxic effect of the infection (17). Bacteriological examinations in sputum, examinations and cytological investigations in terms of mycobacteria, pathogenic fungi, parasites, routine aerobic and anaerobic cultures can be performed. Blood culture is useful in Staphylococus aureus, gram negative bacilli and anaerobe infections. Aerobic and anaerobic culture in pleural fluid is especially useful before initiating treatment in empyema (16). Bronchoscopy is routinely performed in patients who do not respond to antibiotic treatment, have atypical clinical findings, and have abscess with malignant cavity, obstructive tumor and foreign body aspiration (1, 6, 18). In this way, if an endobronchial tumor is seen, a biopsy is taken, the foreign body is removed, drainage is provided with aspiration, an idea is obtained about the localization of the abscess according to the bronchus, and material is taken for bacteriological and cytological examination (6).

Chest x-rays and computed tomography (CT) are used in the diagnosis of lung abscess (1). Lung abscess is recognized by the cavity appearance showing air-fluid level on the chest x-ray (19). Radiography can also be taken in the lateral-decubitus position to better visualize the air-fluid level within the cavitary lesion. Sometimes accompanying conditions such as atelectasis, pneumothorax, pleural thickening may shadow the typical cavity appearance. In addition, if the abscess cavity has drained into

the pleural space, it is possible to see pneumothorax and pyopneumothorax on direct radiography. Computed tomography (CT) of the thorax, which enables the cavitary image to be detected more easily, has become more widely used today (1).

6.Treatment

If a lung abscess is suspected, empirical antibiotic therapy should be initiated. Empirical coverage should target organisms colonized in the upper airway and oropharynx, such as gram-positive cocci, respiratory gram-negative cocci, aerobic and anaerobic gram-negative bacilli (2, 20). Specific treatment is arranged considering the pathogenic microorganism obtained in microbiological research and other accompanying diseases of the patient (21). Catheter drainage of fluid in the abscess cavity and necrotic debris accompanied by bronchoscopy or radiology is another treatment method (22). The suggested combinations of antibiotics for lung abscess are a combination of β-lactam with inhibitors of β-lactamase (ampicillin-sulbactam, amoxicillin-clavulanate, piperacilin-tazobactam), chloramphenicol, second generation of cephalosporins (cefoxitin, cefotetan), imipenem or meropenem, fluoroquinolones-moxifloxacin that is proven to be as effective as ampicillin-sulbactam (1, 23). Empirical treatment is recommended with amoxicillin clavulanate, chloromphenicol or penicillin / metronidozole combination in community acquired acute lung abscesses, since the factors in the etiology are multiple anaerobes and rarely aerobic gram-positive microorganisms (21). Vancomycin or linezolid is preferred for methicillin-resistant Staphylococcus aureus (MRSA). Daptomycin has no efficacy against pulmonary infections (24). For methicillin-sensitive Staphylococcus aureus (MSSA), the choice is cefazolin 2 g IV every 8 hours or nafcillin 2 g IV every four hours or oxacillin 2 g every 4 hours. For methicillin-sensitive Staphylococcus aureus (MSSA) choice is cefazolin 2 g IV every 8 hours or nafcillin 2 g IV every four hours or oxacillin 2 g every 4 hours. Aminoglycosides are not recommended in the treatment of lung abscesses because they pass poorly through the fibrous pyogenic membrane of a chronic abscess. The duration of treatment depends on the clinical and radiological response of the patient (1, 2, 21, 22). Patients should be treated until the fever drops, the Palatinate odor in the sputum and the fluid level in the abscess disappears.The duration of treatment is at least two to three weeks, but usually patients require longer treatment (1, 22, 25). An effective response to antibiotic treatment can be seen after 3-4 days, the general condition improves after 4-7 days, but complete recovery can be seen with radiographic normalization after two months (1). The average closing time of the cavity is 3-4 weeks and can last up to 14 weeks. The average time it takes for the resolution of the infiltration is 8-10 weeks, but it can be up to 24 weeks. Small cavities (smaller than 3 cm) are resolved faster radiologically. The

change in cavity size slows down within 6 weeks after treatment. Cavity size may also indicate ongoing cystic (pneumotoceles) or bronchiectasis changes after treatment. These changes can be detected by bronchography and CT scans. These findings are not an indication for continued treatment or resection (21). Relapse of the abscess is common, especially in cases resistant to drug combinations used initially (22).

An important step in abscess treatment is drainage (1, 26). The presence of air in the cavity of the lung abscess usually indicates that it can be drained without mechanical intervention due to contact with a bronchus. Lung abscess often drains spontaneously into the airways, causing the infection to regress, but can also cause the infection to spread to other parts of the lung. Therefore, chest physiotherapy and postural drainage should be applied to the cases. If the abscess greater than 6 cm in diameter or the symptoms persist for more than 12 weeks with appropriate treatment, the chance of recovery with only medical treatment is very low, and surgical treatment (chest tube drainage or surgical resection of lung abscess with surrounding tissue) should be considered if the general condition allows (26). Endoscopic drainage of lung abscesses is performed during bronchoscopy as an alternative to chest tube drainage (1). Surgical resection of lung abscess is the treatment of choice in approximately 10% of patients. Indications for surgical resection of lung abscess can be divided into acute and chronic. Hemoptysis, prolonged sepsis and febricity, bronchopleural fistula, pyopneumothorax, empyema, abscess rupture are acute indications. Chronic indications are; lung abscess, which is treated unsuccessfully for more than 6 weeks, is defined as cancer suspicion, cavitary lesion larger than 6 cm, and persistent leukocytosis despite antibiotics (1).

7.Complications

Complications are secondary to delay in diagnosis, inadequate treatment, or untreated underlying cause of lung abscess. These include pleural space rupture, pleural fibrosis, restrictive lung disease, respiratory failure, bronchopleural fistula, and pleurocutaneous fistula (8, 12).

8.Prognosis

The mortality of lung abscess has decreased compared to the pre-antibiotic period. The size of the abscess (over 5-6 cm), progressive pulmonary necrosis, obstructive lesions, aerobic bacteria, immune system suppression, old age, systemic debility, delay in medical treatment are factors that increase abscess mortality. Other factors affecting mortality in the patient are anemia, low serum albumin, other diseases, abscess diameter, its location and placement in the right lower lobe (27). When the mortality was evaluated in terms of the agent, it was found that the prognosis was worse in abscesses caused by P.aeruginosa, S.aureus,

K.pneumoniae. Therefore, in abscess cases with such poor prognostic factors, treatment with a rapid aggressive approach is recommended in addition to antibiotherapy (1, 6). Overall mortality in the treatment of lung abscess is approximately 2.0-38.2% with the important role of patient age, malnutrition, comorbidity, immunity, appropriate and timely antibiotics, and supportive treatment (27, 28).

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CHAPTER III

A UNIQUE PANDEMIC: COVID-19

Aydın Kant

(Dr.), Trabzon Vakfıkebir State hospital, Trabzon, Turkey, e-mail: aydinkant@yahoo.com

ORCID *0000-0003-2914-2478*

1.Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global public health problem that is causing a worldwide epidemic, currently unable to be effectively treated because there is no specific antiviral drug, and early detection of medical isolation is extremely important. It was named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) and declared a pandemic on March 11, 2020 (1, 2). COVID-19 ranges from asymptomatic or cold-like symptoms such as dry cough, fever and fatigue to severe dyspnea and respiratory failure. It has been reported that COVID-19 disease has a more serious clinical course risk in patients with comorbidities such as hypertension, diabetes, and cardiovascular disease (3). Since the first reported COVID-19 case in Wuhan, China at the end of 2019, COVID-19 has rapidly spread throughout China and then to all countries of the world. As of January 01, 2021, more than 84 million cases have been confirmed worldwide and over 1,800,000 deaths (4).

2.Etiology

Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family of Coronaviridae in the order Nidovirales, and this subfamily including α-coronavirus, β-coronavirus, γ-coronavirus, and delta-coronavirus (5). Coronaviruses are generally not very resistant to the external environment. The durability period in the outdoor environment varies depending on factors such as the humidity and temperature of the environment, the amount of organic matter expelled, the texture of the contaminated surface. (2, 3). Coronaviruses primarily cause infections in birds and mammals. It has been seen to infect humans in recent years. The severe acute respiratory syndrome (SARS) outbreak in 2002 and the Middle East respiratory syndrome (MERS) outbreak in 2012 showed that coronaviruses are fatal when they infect humans (6). SARS CoV-2, which causes COVID-19 disease detected at the end of 2019, has also been shown

to have a typical coronavirus genome structure and belong to the β - coronavirus cluster, including SARS - CoV and MERS - CoV (7).

3.Transmission

Most research conducted in Wuhan at the beginning of the outbreak has shown that the first patients worked or visited a market selling seafood in Wuhan. As the outbreak progresses, it has been shown that this viral infection is transmitted from person to person through droplets and through infected surfaces or contaminated hands (8). The virus can be found in the respiratory secretions of patients 1-2 days before the onset of clinical symptoms and two weeks after the symptoms of the disease (9, 10).

4.Clinical and epidemiological features

Some of the COVID-19 patients may be asymptomatic, while others may have a wide variety of symptoms such as fever, cough, shortness of breath, myalgia, fatigue, headache, diarrhea, nausea, vomiting, loss of smell and taste (9, 11-14). The most common symptoms of infection are fever, fatigue and dry cough (12). Clinical symptoms differ according to age and gender (12, 13). All ages of the population are susceptible to SARS-CoV-2 infection and the average age of infection is approximately 50 years (12). In general, males over 60 years of age with comorbidities are more likely to develop severe respiratory disease requiring hospitalization and even death (12). However, most young people and children have only mild diseases or are asymptomatic (12, 14).

In a study by Chen et al, examining 99 patients hospitalized with the diagnosis of COVID-19 in the same hospital, they showed that the possibility of being infected is higher in elderly men and that they rapidly enter acute respiratory distress syndrome (ARDS), which creates a life-threatening situation (15). In a study where comorbidities were analyzed, it was shown that approximately 17% of the patients had hypertension, 8% had diabetes, 5% had cardiovascular diseases and 2% had respiratory system diseases (16). It has been reported that mild cases recover within 1 week and progressive respiratory failure resulting in death in severe cases may develop (14). It has been determined that most deaths from COVID-19 include cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer (10). In a study in which 72,314 cases were examined, it was reported that 81% of mild cases, 14% of severe cases requiring intensive care support, and 5% of critical cases with respiratory failure, septic shock and / or multi-organ dysfunction (17).

COVID-19 is a prothrombotic condition that causes both microvascular and macrovascular thromboembolic events and particularly pulmonary embolism in pulmonary and extrapulmonary organs (18). Thrombosis in COVID-19 patients is thought to be mainly due to

angiotensin converting enzyme-2 receptor-mediated endothelial damage. Endothelial damage causes macrophage activation syndrome, which leads to cytokine storm, intussusceptive angiogenesis and activation of the coagulation cascade (18-20).

The fact that WHO evaluated the R_0 value between 1.4 and 2.5 and affected approximately 84 million people by the last day of 2020 indicates the difficulty of controlling the epidemic (4, 21, 22). The high transferability of SARS-CoV-2 can be attributed to the unique virological properties of SARS-CoV-2, its ability to stay on non-living surfaces for days, and the presence of high viral load in upper respiratory tract samples during the initial phase of the disease (23, 24). The COVID-19 patient spreads the viruses in liquid droplets during conversation. However, smaller and much larger numbers of particles known as aerosol particles can also stay in the air for a long time and then penetrate deep into the lungs when inhaled by someone else (25, 26). This explains the rapid geographic spread of COVID-19. Strict compliance with infection control measures in both the community and hospitals and the introduction of COVID-19 vaccines into clinical use seems to be the only way to control the disease.

5.Diagnosis

Early diagnosis is very important to prevent COVID-19 disease (27). The gold standard in diagnosis is the rRT-PCR test positivity. However, COVID-19 cannot be excluded with a negative result of the RT-PCR test for SARS-CoV-2 in patients with clinical and epidemiological features compatible with COVID-19 infection. Poor sample quality, too early or too late sample collection time, incorrect storage and handling of samples, and virus mutations have been reported to cause false negative results (28). Since false negative results play an important role in the spread of the infection, alternative diagnostic methods are needed. At the onset of the COVID-19 outbreak, diagnosis was based on clinical features and thoracic imaging (29). Normal chest radiography does not exclude the disease, since the sensitivity of conventional chest radiography in thoracic imaging is 30-60% (30). Computed tomography (CT), another method used in thoracic imaging, has a higher sensitivity than lung radiography. Therefore, it has been reported that CT can be used as the first imaging technique in patients with high clinical suspicion for COVID-19 (31). Kant et al. showed that in patients with positive rtRT-PCR test, CT was positively correlated with the age and symptom duration of the patients (32). They reported that patients over 60 years of age with clinical and epidemiological findings consistent with COVID-19 were 7.17 times more likely to have CT findings (32). Typical imaging features of patients with COVID-19 are reported to have different features at different stages of the disease (31). While ground-glass opacity is seen in the initial stage of the

disease, other patterns such as pulmonary consolidation and paving stone appearance can be seen in the later stages (33, 34). In the studies of Kant et al., the CT positivity rate was 85.1% in patients with symptom duration longer than two days. In the examination of this parameter with ROC analysis, the area under the curve was reported as 0.869, sensitivity as 90.5% and specificity as 76.2% (32). Bernheim et al. showed that the CT finding was not sufficient for diagnosis in the first two days of the disease, but it had a diagnostic value in the following days (35). In the study of Kostakoğlu et al., they stated that rtRT-PCR positivity was associated with clinical findings (36). In this study, it was reported that age (<60), symptom duration less than 5 days, presence of headache and absence of shortness of breath correlated with rtRT-PCR positivity (36). In the studies of Guo et al., it was reported that the PCR positivity rate after the onset of symptoms was more than 90% in 1-3 days, less than 80% in the 6th day and less than 50% after 14 days. In this study, the PCR detection rate was higher than IgM ELISA before 5.5 days after the symptom onset, and the positivity rate of IgM ELISA was higher than the PCR method after 5.5 days (37). All these studies revealed that rtRT-PCR is not a reliable and independent test for COVID-19 screening. CT was found to be positively correlated with patients' age, symptom duration, comorbid disease, shortness of breath, and fever. It should be kept in mind that the negativity of the rtRT-PCR test does not rule out the diagnosis of COVID-19 in patients with symptom duration> 5 days, elderly, with comorbid disease and especially fever and shortness of breath. Typical CT findings for COVID-19 in these patients are diagnostic. If the first rtRT-PCR test is negative or the test is not performed, it is important for public health to diagnose patients according to CT imaging in order to prevent the spread of infection. Similarly, in patients with new onset symptoms, normal chest CT should not cause disruption of isolation measures until the PCR test is available.

6.Treatment

There is no specific treatment for COVID-19. Symptomatic treatment is recommended for mild cases that progress as uncomplicated respiratory tract infections and do not require hospitalization (38, 39). In addition to supportive treatments such as oxygen therapy, intensive care, mechanical ventilation, treatments such as antivirals, antibiotics and steroids are also used in Covid 19 patients (38-40). Unfortunately, standard treatment against COVID-19 is currently lacking. Supportive care is important since there is no standard treatment regimen for COVID 19 treatment. In addition to conventional oxygen therapy, case series have been published dealing with prone positioning in awake and spontaneously breathing patients. It is unclear whether this measure will permanently improve oxygenation or prevent a possible intubation. However, it is stated

that the prone position reduces the need for intubation. Oxygen therapies applied with high-flow nasal cannulas (HFNC) can also be effective in clinically stable patients (41). Although the evidence for the benefit of using HFNC and non-invasive ventilation (NIV) is poor, these treatment modalities appear to be important in terms of avoiding intubation and prognosis. However, the treatment of these patients in the intensive care unit presents great difficulties for the entire treatment team (41).

Scientists around the world continue to simultaneously investigate the effectiveness of existing drugs against SARS-CoV-2, as well as developing new treatment options. And these drugs are used in the treatment of patients. The mechanisms of action of the drugs recommended for use in the guidelines are to prevent the entry of the virus into the cell, to reduce or inhibit its replication, and to suppress the increased and uncontrollable inflammatory response caused by the disease. It is aimed to neutralize the virus with immune plasma treatments that contain antibodies against the virus obtained from healed patients (42). For this purpose; convalescent plasma, immunomodulatory drugs (Chloroquine and Hydroxychloroquine, Azithromycin), RNA dependent RNA polymerase inhibitors (Favipiravir, Remdesivir, Ribavirin), protease inhibitor (Lopinavir / Ritonavir, darnunavir), Interleukin (IL) -6 inhibitor (Tocilizumab), Interleukiline -1 (IL-1) receptor antagonist (Anakinra) and other drugs (dexamethasone, prednisolone, Ivermectin, Teicoplanin and lipoglycopeptides, Oseltamivir and Baloxavir) are used (43, 44). There is insufficient evidence regarding the safety and efficacy of these treatments. In addition, there are non-virus-specific (such as low molecular weight heparin) treatment regimens used to prevent disease-related complications (45).

As a result, there is no specific drug or vaccine treatment yet for the new coronavirus. Given the spread of this virus and the increasing number of infected people, the COVID-19 pandemic will continue to be a major problem around the world. In pandemic control, the most important points are the prevention of transmission routes with the measures taken in the society, determination of patients and contacts, treatment and follow-up, isolation, hospital facilities and adequate treatment services. This pandemic should be managed by all countries, in line with epidemiological data and by using a suppression method, with an approach focused on preventing cases and deaths.

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CHAPTER IV

DO NOT RUSH TO REPORT NEWS OF THE DEATH: LAZARUS PHENOMENON

Ali Gur

(Asst. Prof. Dr.), Ataturk University, Erzurum, Turkey.
e-mail: doktoraligur@gmail.com
0000-0002-7823-0266

1.Introduction

Lazarus is a Gospel who returns from the dead by Jesus. Lazarus phenomenon, or autoresuscitation, is the spontaneous return of circulation (SROC) after failed cardiopulmonary resuscitation (CPR) efforts (1). The first case report was made in 1982 (2). In a study conducted in 2014, it was reported that the number of cases increased to 38 (3). We aimed to present the Lazarus phenomenon developing after CPR in a patient of chronic obstructive pulmonary disease (COPD).

2.Case

A 65-year-old male patient was admitted to the emergency department by ambulance due to COPD exacerbation. He was unconscious. No pulse was felt while the patient was on a stretcher. CPR was started immediately and effective chest compressions were achieved. Resuscitation protocols were applied to the patient. Every 3 minutes, 1 mg adrenaline was administered to the patient. Endotracheal intubation was performed. Oxygenation was started. Every 15 minutes, patient relatives were informed about the procedures. The pulseless electrical activity ended after 45 minutes CPR, asystole has occurred and CPR was terminated. The patient was considered dead. 5 minutes after the decision of death, her breathing effort was returned while we are preparing to say the patient's dead news. The nodal rhythm was seen again. The carotid and femoral pulse were palpated for 10 seconds. Then the patient were examined in detail. The patient's blood gas values were as follows; ph: 7.12, pCo_2:65 mmHg, pO_2: 40 mmHg. The patient was diagnosed with COPD exacerbation. The patient was connected to the mechanical ventilator. The treatment was started in the emergency room. Intravenous 120 mg methylprednisolone and 40 mg ulcuran were administered to the patient. Chest diseases consultation was requested. The patient was hospitalized in intensive care unit of chest diseases. Treatment of the patient was

continued in the intensive care unit of chest diseases. 2 days later, the patient became ex in intensive care unit.

3.Discussion

Although only a handful of such cases have appeared in the literature, there has been speculation that the Lazarus phenomenon occurs more often than those few reports would suggest (4). Various mechanisms have been suggested as explanations for the phenomenon. Bradbury (5) suggested delayed delivery to the heart of previously administered adrenaline as the basis for SROC in a patient after acute myocardial infarction and left ventricular failure. Voelckel and Kroesen (6) reported a case of suspected hyperkalemic cardiac arrest and hypothesized that SROC seven minutes after discontinuing the resuscitation was attributable to a gradual intracellular shift of potassium after previously administered bicarbonate. In our case, we don't know which mechanisms were occurred.

Hyperventilation, COPD, alkalosis, hyperkalemia, hypothermia, hypovolemia, delayed effects of drugs, minimal vital signs, such as unnoticed conditions cause the Lazerus phenomenon (7). In our case, the patient was a COPD patient and COPD was considered as the cause of the Lazarus phenomenon.

To diagnose death, there should be no consciousness and breathing, no pulse, no pupillary reflexes, and asystole should be seen on the monitor. With these findings, it is recommended to wait for another 5 minutes in order to be able to say the patient exitus as an exact exitus. As the hour of death, it should be recorded at the end of this 5-minute period (8). In our case, the patient had no breathing, circulation and pupil reflex. At electrocardiogram the patient was asystole. However, the patient's spontaneous circulation and breathing came back after 5 minutes close to reporting his death.

4.Conclusion

After 5 minutes of cardiorespiratory arrest, the pupillary response to light, the corneal reflex, and the motor response to supra-orbital pressure should be evaluated before the explanation of death to the patient's relatives.

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CHAPTER V

RELATION BETWEEN REPOLARIZATION PARAMETERS AND STROKE LOCALIZATION IN ACUTE ISCHEMIC STROKE

Unal Ozturk[1*] & Onder Ozturk[2]

(MD), *H ealth Sciences University of Turkey, Diyarbakir Gazi Yasargil Education And Research Hospital, e-mail: drunalozturk@gmail.com*

ORCID *0000-0002-8341-5070*

** Corresponding Author*

(Assoc. Prof. MD.), *Health Sciences University of Turkey, Diyarbakir Gazi Yasargil Education And Research Hospital, e-mail: droozturk21@hotmail.com*

ORCID *0000-0003-4204-0599)*

1. Introduction

Acute stroke is an important cause of morbidity, and mortality and cardiovascular complications are common after an acute stroke (1) (2) . Several ECG abnormalities have been reported in patients following acute cerebrovascular events including QT interval prolongation, ST-segment deviation, and T-wave changes (3). The insula is assumed to play a central regulatory role for the autonomous nervous system. Autonomic nervous system dysregulation after acute cerebrovascular events possibly causes sympathetic activation resulting in cardiac arrhythmia. Ventricular repolarization abnormalities play an important role in the occurrence of arrhythmia. QT dispersion, a marker of repolarization homogeneity, is considered a predictor of sudden cardiac death and mortality in patients with acute ischemic stroke. Despite some controversial data about the positive predictive value of increased QT dispersion, this ECG marker appears to be a powerful tool for risk stratification in patients with impaired left ventricular function after acute ischemic stroke. The T wave is generated by myocardial voltage gradients during the repolarization phase of cardiomyocyte action potentials. QT interval is a measure of repolarization duration, but may not reveal other changes during the repolarization process. T-wave peak to T-wave end (TPE) interval measures terminal repolarization, and has experimentally been linked to arrhythmogenic repolarization dispersion in the myocardium (4). In this study, we aimed to investigate the

relationship between repolarization parameters and stroke localization in acute ischemic stroke patients.

2. Materials and Methods

Study participants and design

Patient Selection

A total of 213 patients (116 men, 97 women, 68 ± 15 years) with acute ischemic stroke were included in the study. Patients were divided into 4 groups according to the clinical ischemic classification (Group 1 (Total anterior circulation infarcts) , n=19 ; Group 2 (Partial anterior sirculation infarcts), n=73; Group 3 (Lacunar infarcts), n= 83 ; Group 4 (Posterior circulation infarcts), n=38. Demographic and baseline clinical data, including neurological deficit severity assessment with NIHSS on admission to the neurology care unit were recorded. Patient clinical data, history of cardiovascular risk factors, and stroke onset were determined, and neurologic examination was conducted at the time of admission. The diagnosis was made based on the neurologic examination and cranial imaging within 24 h of symptom onset. Neuroimaging included description of stroke type, stroke location, and insular involvement. All patients underwent immediate computed tomography after being admitted to the emergency care unit. Troponin levels were measured and electrocardiogram (ECG) was recorded after admission to the neurology care unit. The study was approved by the Ethics Committee of our hospital and informed consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Analysis of QT, Tpe interval

All standard 12-lead ECGs were recorded at 25 mm/s speed and 10 mm/mv gain with Nihon Kohden ECG-9132K electrocardiograph (Nihon Kohden Corporation, Tokyo, Japan). A 12-lead resting ECG was recorded at admission in the neurology care unit for patients with an acute ischemic stroke and then was manually measured with a ruler. All ECGs were manually analyzed by an experienced cardiologist who was unaware of the clinical data. The QT interval was measured from the beginning of the QRS to the end of the T-wave. The end of the T-wave was defined as the point of return to the isoelectric line (5). In cases where the T-wave was interrupted by a U-wave, the end of the T-wave was defined as the nadir between the T- and U-waves. In instances where the T-wave could not be reliably determined due to extremely low voltage (<0.1 mV), measurement of QT interval was not established and consequently, these leads were excluded from the analysis. In order to exclude the effects of the heart rate (HR) on the QT interval, the QT interval was corrected according to the Bazett formula (QTc = QT/square

root of RR interval). QTd was defined as the difference between the maximum and minimum QT intervals. T peak to T end (Tpe) was measured with a ruler from the peak of the T-wave to its end; Tpe was corrected for heart rate. The criteria to determine the endpoint of the T-wave were similar to the aforementioned criteria considered for the QT measurement (5).

Definition of stroke and assessment of stroke severity

According to the updated definition of stroke in the American Heart Association/American Stroke Association guidelines, ischemic stroke is diagnosed based on the combination of symptoms and/or signs of typical neurological dysfunction and imaging evidence of central nervous system infarction. Therefore, ischemic stroke is defined as a neurological dysfunction episode caused by focal cerebral, spinal, or retinal infarction on imaging. NIHSS is a simple, valid, and reliable systematic assessment tool that measures acute stroke-related neurologic deficit (6). The NIHSS score is a very important scale for clinical assessment as it enables the determination of appropriate treatment,prediction of lesion size, measurement of stroke severity, and prediction of patient outcome in patients with acute ischemic stroke. The NIHSS comprises 11 different elements evaluating specific ability. Each ability is scored between 0 and 4, where 0 corresponds to normal functioning and 4 corresponds to complete impairment. A patient's NIHSS score is calculated by adding the score for each element of the scale; 42 is the highest score possible. A higher NIHSS score corresponds to greater impairment of cerebral function in a stroke patient.

The higher the NIHSS score, the higher the impairment of a stroke patient. According to NIHSS score, there are five stroke severity groups: NIHSS = 0 (no stroke), NIHSS = 1–4 (minor stroke), NIHSS = 5–15 (moderate stroke), NIHSS = 16–20 (moderate-to-severe stroke), and NIHSS = 21–42 (severe stroke). A baseline NIHSS score greater than 16 indicates a strong probability of patient disability and death (6). Stroke severity at admission to the neurology care unit was assessed by the NIHSS score by a neurologist. Patients were categorized into two groups; Group 1 comprised of patients with nonsevere stroke (NIHSS <16; n = 69), whereas Group 2 comprised of patients with severe stroke (NIHSS ≥16; n = 27).

Statistical analysis

Statistical analysis was conducted with the SPSS statistical package (Version 12.0; SPSS Inc., Chicago, IL, USA). All baseline parameters were analyzed. Continuous variables are expressed as mean ± SD and categorical variables are expressed as percentages. Intraobserver variability was calculated as the absolute difference between the two

measurements as a percentage of their mean. Mann–Whitney U test and Chi-square test were used for comparison of data as appropriate. P values < 0.05 were considered statistically significant. Spearman's correlation was used to determine the relationship between NIHSS and clinical parameters.

3. Results

Baseline characteristics

The baseline characteristics of patients are summarized in Table 1. Clinical characteristics of groups were similar with respect to age, gender, hypertension, diabetes, smoking ($P > 0.05$).

Electrocardiographic findings

QTc, QTd, QTcd, Tpe values were significantly higher in Group 1 and Group 2 patients than Group 3 and Group 4 patients (Table 2).

Correlation analysis performed to investigate the relationship between NIHSS score and clinical parameters showed a positive correlation between the NIHSS score and QTc, QTd, Tpe, Tpe/QT, age. (Table 3).

4. Discussion

Acute stroke is characterized by profound autonomic dysregulation, including alterations in the autonomic reflex pathways, central autonomic neuroanatomical sites, and hormonal factors (7). Stroke-related sympathetic activation is high in patients with higher NIHSS scores. There is a relationship between the central nervous system and the cardiovascular system during acute cerebrovascular disease (8). The previous studies have reported that a relationship between acute cerebrovascular disease and QT (4) (9). The effect of cerebrovascular events on the cardiovascular system is due to neurogenic myocardial stunning and changes in the autonomic nervous system (increased sympathetic control, reduced parasympathetic control). Significant imbalances between the repolarization and depolarization and of the heart may be associated with arrhythmic conditions. Lazar et al. found that a positive relationship between baseline QTd and NIHSS and modified ranking scores (10). Afsar et al. could not find any differences in the QT dispersion values between rightand left-sided strokes in the 24-hour ECGs (11). In the study by Sander and Klingelhöfer , right-sided infarcts more frequently showed QT prolongation and arrhythmias than left-sided infarcts (12). In a study performed by Colivicchi et al., right insular infarcts were associated with more complex arrhythmias (13). Tokgozoglu et al. concluded that stroke in the region of the insula, especially the right, leads to a decreased heart rate variability (14).

Stead et al. found an increased risk of early death in patients with acute ischemic stroke and a prolonged QTc interval at the time of emergency department presentation (15). Marafioti et al. found that the QTc interval prolongation is mainly a marker of serious cerebral damage (16). Villa et al. found that in patients with ischemic stroke and prolonged QTc interval, the risk of dying could be significantly higher than in patients with normal QTc interval (17). In our study, we found that QT was significantly higher in Group 1 and Group 2 patients than Group 3 and Group 4 patients. Christensen H and et al found that, insular damage, especially right sided insular damage was related to ECG changes in patients with acute stroke. Right insular lesion predicted death within three months of stroke independent of age, severity of stroke, and infarction volume. Patients with insular involvement significantly more often presented with ECG abnormalities(18).

The previous study found that a significant association between changes in QTd and stroke severity quantified by the National Institute of Health Stroke Scale (NIHSS) (19). Larger stroke lesions were associated with greater QTd in the early stages of stroke in the 2 studies (11) (20). Simula et al. found that right MCA ischemic stroke results in prolongation of QT interval (21).

Hypertension, hyperlipidemia, and diabetes mellitus are important risk factors for atherosclerotic cerebrovascular disease. However, Bonardo et al. found that, in young patients with acute ischemic stroke, large infarct volume was not associated with high blood pressure at admission (22). Hendrix et al. found that diabetes mellitus history is an important predictor of stroke severity (23).

5. Conclusions

Our results suggested that, repolarization parameters are associated with stroke localization on admission in patients with acute ischemic stroke. Repolarization parameters can help to evaluate arrhythmia risk in patients with acute neurologic diseases.

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Table 1:Clinical characteristics of patients.

Variables	Group-1 (Total anterior circulation infarcts) n=19	Group-2 (Partial anterior circulation infarcts) n=73	Group-3 (Lacunar infarcts) n=83	Group-4 (Posterior circulation infarcts) n=38	p Value
Age (year)	70.1 ± 12.3	68.7 ± 12.9	68.3± 11.9	69.3± 9.4	NS
Gender (F/M)	11 / 8	41 / 32	38/45	21/17	NS
Hypertension	8 (42%)	34 (45%)	48 (57%)	16 (42%)	NS
Diabetes Mellitus	5 (26%)	19 (26%)	21 (25%)	8 (21%)	NS
Smoking	5 (36%)	20 (32%)	29 (34%)	13 (34%)	NS
Dyslipidemia	6 (31%)	17 (26%)	23 (27%)	11 (28%)	NS

Table 2: Electrocardiographic parameters of patients.

Variables	Group-1 (Total anterior circulation infarcts) n=19	Group-2 (Partial anterior circulation infarcts) n=73	Group-3 (Lacunar infarcts) n=83	Group-4 (Posterior circulation infarcts) n=38	p Value
QTc (ms)	541±75.2	532±76.7	476±48.9	485±53.4	<0.05
QTd (ms)	91.7±3.9	92.4±5.3	61.8±3.1	66.7±3.7	<0.05
QTcd (ms)	95.9±4.3	96.4±3.6	66.2±3.7	67.6±3.7	<0.05
Tpe (ms)	96.3±4.7	95.1±3.5	64.5±3.1	66.4±3.8	<0.05
Tpe / QT	0.18±0.029	0.18±0.032	0.13±0.025	0.14±0.026	<0.05

Table 3: Correlation between NIHSS score and clinical parameters in patients with acute ischemic stroke

Parameters	**Pearson's correlation coefficient (r-value)**	**P-value**
QTc	0.342	0.037
QTd (ms)	0.297	0.032
Tpe (ms)	0.346	0.040
Tpe / QT	0.258	0.043
Age	0.320	0.036
* NIHSS: National Institutes of Health Stroke Scale,		

CHAPTER VI

PEDIATRIC STIFF MAN SYNDROME WITH TYPE-1 DIABETES MELLITUS

Rabia Tutuncu Toker

(MD), Pediatric Neurologist, Department of Pediatrics, Division of Pediatric Neurology, Bursa City Hospital, Bursa, Turkey, e-mail: rtutuncutoker@gmail.com

0000-0002-3129-334X

Stiff man syndrome (SMS), also known as stiff person syndrome, was first described by Moersch and Woltman in 1956 for stiffness and spasms of the extremities and axial muscles. Over time, variant forms of this syndrome such as paraneoplastic SMS, rigid limb syndrome, and progressive encephalomyelitis with myoclonus and rigidity have been identified. Solimena et al. indicated a relationship between the disease and glutamic acid decarboxylase antibody (anti-GAD) positivity and type 1 diabetes mellitus(T1DM) (McKeon, 2012)(Clardy et al., 2013)(Solimena, Folli, Aparisi, Pozza, & De Camilli, 1990). SMS is very rare in children (Clardy et al., 2013). In this article, a case of pediatric SMS with symptoms of walking difficulty, lower extremity stiffness, and involuntary movements is presented.

1. Case

A 9-year-old male patient was admitted to hospital with the symptoms of contraction in both legs, involuntary movements, and difficulty in walking. He had a history of contraction in his left leg two days previously and he fell from a ladder while he was conscious, and then had difficulty in walking due to pain in his waist and leg. He was admitted to another hospital's emergency department, radiographs were obtained and the results were normal. He was discharged with analgesic treatment only. He experiences contraction in both legs and inability to walk when he wakes up the next morning. He described tenderness in the lumbar region. Both legs occasionally formed a dystonic posture and he described severe pain at these times. In his medical history, he had been followed up for a year with the diagnosis of T1DM and is receiving insulin treatment. The family history was unremarkable. Physical examination revealed spasm and tension in both leg muscles that increased with palpation. A neurologic examination revealed that deep tendon reflexes were normactive. Plantar response was bilateral flexor, and clonus was not

observed. The strength of proximal and distal muscles was normal in the extremities, but with stiffness in the thoracolumbar muscles. Cranial nerve examination, cerebellar tests, and sensory examination were normal. Anal sphincter reflex was normal. Laboratory tests revealed normal hemogram, blood glucose, liver, and kidney function tests, and electrolytes (sodium, calcium, potassium and magnesium). Creatinine phosphokinase level was found to be 1447 IU / L (upper limit of 210 IU / L). The thyroid function tests were normal, antinuclear antibody and anti-helix DNA antibody were positive, and the anti-GAD level was 1000 IU/L (<1 IU/L). Chest X-ray, abdominal and thorax ultrasonography, peripheral smear, and tumor markers were normal. On the first day, the patient underwent spinal and cranial magnetic resonance imaging (MRI) in case of any possible spinal trauma and MRI resulted as normal. Focal seizures were considered because of the intermittent stiffness and spasms. Electroencephalography (EEG) was performed and found to be normal. The contractions in the legs increased when he got excited when healthcare staff entered the room or when he wanted to move. Baclofen (body weight 22 kg) 30 mg/day and sertraline 25 mg/day were started as treatment. However, the spasms in the lower extremity muscles increased and began to progress to the hip and axial muscles. On the third day, needle electromyography (EMG) was applied to the lower extremity muscles, which showed continuous spontaneous discharges with neurogenic motor unit potentials (MUP) in bilateral lower extremity muscles. Findings were considered as neurogenic MUP changes and spontaneous continuous muscle contraction in lower extremity muscles. The patient was diagnosed as having SMS based on the clinical and EMG findings. On the fifth day, although baclofen (100 mg/day) was maximized, clonazepam was added to the treatment due to the lack of response. An initial dosage of clonazepam 0.5 mg/day was given and then increased by 0.5 mg every day. The maximum 2 mg/day clonazepam was given on the eighth day. The patient benefited from clonazepam. The spasms regressed and he started to walk again within a week and discharged from the hospital.

2. Discussion

SMS is not well recognized, even in the adult age group, and can be missed in the pediatric age group (Clardy et al., 2013). SMS is characterized by increased spasms and lumbar lordosis, especially in the axial muscles and lower extremity muscles. The spasms increase with tactile, acoustic or emotional stimuli(H. M. Meinck et al., 1994) . Classic SMS (adult and child) occurs with stiffness and spasms in the lumbar region and lower extremities, but there are other forms of SMS such as isolated extremity or body rigidity, and progressive forms of encephalomyelitis have been described. Diagnosis is made through clinical findings (Clardy et al., 2013)(H.-M. Meinck, 2001). In our case, spasms

were increased when the patient was excited by healthcare staff entering the room, but this suggested psychical causes too. In our case, contractions first started in the lower extremity and progressed to axial muscles over time.

Although the etiology of SMS is not known, its association with autoimmune diseases shows that autoimmune mechanisms play a role. Gamma-aminobutyric acid (GABA) is a major inhibitory transmitter and GAD plays role in the synthesis of this transmitter. The role of autoimmunity against GAD is not yet understood because the same antibody is found in different autoimmune diseases (H.-M. Meinck, 2001). Anti-GAD positivity is frequently reported, especially in patients with T1DM, Hashimoto thyroiditis, Graves' disease, and myasthenia gravis (Clardy et al., 2013)(Solimena et al., 1990)(Baizabal-Carvallo, 2019)(Dayalu & Teener, 2013). Anti-GAD positivity in patients with SMS is found in 80% of cases (Clardy et al., 2013). The anti-GAD level was found to be high in our patient who had T1DM. It is unclear why some autoimmune diseases with the same autoantibodies accompany SMS. However, different antibodies such as amphiphysin or glycine receptor, especially those described in adults with SMS, are also known (Clardy et al., 2013). It is reported that paraneoplastic SMS may occur in some adult malignancies such as lymphoma and lung cancer (Jun et al., 2015). Therefore, our patient was examined for malignancies and no sign of any malignancy was detected. It has been reported that baclofen, benzodiazepines (diazepam, clonazepam), steroids, plasmapheresis, intravenous immune globulin, and rituximab can be used in the treatment of SMS (Clardy et al., 2013; Rineer & Fretwell, 2017; Sarva, Deik, Ullah, & Severt, 2016). Our patient did not respond to baclofen, but significant improvement was observed after benzodiazepine use. Although autoantibody positivity was high, immune regulators were not necessary in our case.

In conclusion, SMS should be considered in the differential diagnosis in patients with muscle stiffness and increased spasms induced with stimulus. Care should be taken in terms of accompanying autoimmune diseases and malignancies in these patients.

Learning Points:

• Symptoms of SMS such as stiffness and spasms, especially in the lower extremities, cause gait difficulties.

• Autoimmune disorders such as type 1 diabetes mellitus can coexist with this syndrome. The relationship is not well understood.

• Treatment include benzodiazepines (e.g. diazepam, clonazepam) and immunotherapies (e.g. immunoglobulin, plasmapheresis, steroids. We obtained a good response to clonazepam.

Written informed consent was obtained from the parents for publication.

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CHAPTER VI

CLINICAL AND TREATMENT CHARACTERISTICS OF PARANASAL SINUS AND NASAL CAVITY CANCERS

Ozgur Tanriverdi[1] **& Turan Karaoglu**[2]

[1](Assoc. Prof. Dr.), Mugla Sitki Kocman University, Deparment of Medical Oncology, Mugla, Turkey, e- mail: dr.ozgur.tanriverdi@gmail.com

ORCID 0000-0002-0598-7284

[2](Dr.), Mugla Sitki Kocman University, Mugla, Turkey
e- mail: turan_karaoglu@hotmail.com

ORCID 0000-0002-6318-8560

1. Introduction

Paranasal sinus and nasal cavity cancers are very rare and constitute approximately 3% of all head and neck malignancies (1-3). They constitute a highly heterogeneous group of malignancies in terms of both localization and histological type (1,3). Although distant metastasis and lymph node involvement are not common, topographic anatomical features have some difficulties in local treatment because of the functional and vital features of the surrounding structures and local recurrence rates are quite high (1-4).

Multidisciplinary oncological approach with pre-treatment evaluation and staging is very important in treatment plans of patients with paranasal sinus and nasal cavity cancer (1,4). As with other head and neck cancers, the most effective and important treatment approach that contributes to survival in patients with both paranasal sinus and nasal cavity cancer is the initial treatment option. Because even if salvage surgery or salvage radiation treatments are successful in suitable patients, the first treatment plan has been reported to be more effective especially in local disease (5-8). Often, progressive outcome of initial treatment failure occurs within the first 2 years of diagnosis. Therefore, it is very important that the patients are closely followed up especially during the first 2 years (5, 7-9). In addition; almost 33% of these patients develop a second primary cancer in the respiratory and gastrointestinal tracts. Because of this risk, it is important to follow up and evaluate patients with paranasal sinus cancer for second primary cancers (1,2,4,8).

This article includes the current literature on the clinical and therapeutic features of paranasal sinus and nasal cavity cancers that do not have adequate treatment and prognosis data due to their rarity.

2. Epidemiological and histopathological features

Nasal cavity and paranasal sinus cancers, which are frequently considered together, are often diagnosed as advanced stage disease and have a poor prognosis (5,7,8). According to the literature information, it is more common in men than in women (1,2,4).

Squamous cell carcinoma accounts for approximately 70-80% of all paranasal sinus and nasal cavity cancers. Adenocarcinoma is the majority of the remaining histological subtypes (1,4). In squamous cell carcinoma, the tumor mass often grows into the bone structures of the sinuses and often remains asymptomatic unless erosion or invasion into adjacent structures (1,4,6).

Minor salivary gland tumors (adenoid cystic carcinoma, adenocarcinoma and mucoepidermoid carcinoma) account for approximately 10-15% of paranasal sinus and nasal cavity cancers, except squamous cell carcinoma (9-12). Malignant lymphomas constitute approximately 5% of all cases, while malignant melanoma, poorly differentiated carcinoma, angiosarcoma, rhabdomyosarcoma and olfactory neuroblastoma (esthesioneuroblastoma) are seen in less than 1% of patients (9-13).

Paranasal sinus cancers most commonly develop from the maxillary sinuses (6,11). While cancers of the ethmoid sinus, nasal vestibule and nasal cavity are less common, cancers of the sphenoid and frontal sinuses are very rare (6,8,11).

The features of paranasal sinus cancers are not frequent nodal involvement in the early stages (6,9,11). For sinus malignancies, the first step of lymphatic drainage is the retropharyngeal lymph nodes. In addition, depending on the location of the primary tumor, periparotid, cervical 1B and 2 level lymph nodes are also frequently involved. The main lymphatic drainage of the maxillary sinus is the first station via submandibular, parotid and jugulodigastric lymph nodes, lateral and inferior trunks, and retropharyngeal and jugular nodes superoposterior trunks (9). The frequency of lymph node involvement in paranasal sinus cancers varies depending on the local spread of the primary tumor to the surrounding structures (9,11). Lymph node metastasis is more common in T2 tumors than squamous cell carcinoma of maxillary sinus than T3 or T4 tumors (9,12).

Distant metastasis occurs rarely at the time of diagnosis and after primary treatment, but lung, liver and bone are the most common sites of metastasis (1,9,11). Even though distant metastasis develops in 20-40% of both nasal cavity and paranasal sinus cancer patients, these patients often die due to the direct spread to important structures in the skull due to rapid progression of regional and local disease (9,11).

3. Etiology and risk factors

It has been reported that the most important etiological factor in cancers of paranasal sinuses and nasal cavity is exposure to some industrial substances such as leather industry, textiles, wood dusts, formaldehyde, and tobacco exposure (6,14). It is thought that the incidence of second primary head and neck tumors is increased in patients at this risk (7,11).

It has been reported that some of the patients with paranasal sinus and nasal cavity squamous cell carcinoma are associated with human papilloma virus [HPV] and HPV positive patients have a better prognosis than HPV negative ones (14,15). There are studies showing the association of HPV with malignant degeneration of inverted papilloma, which is a rare and generally accepted benign condition (15). Similarly, there is a relationship between Epstein-Barr virus infection and sinonasal lymphomas (16).

4. Clinical features

Paranasal sinus malignancies are usually asymptomatic until they invade into neighboring structures or present with nonspecific symptoms resembling benign diseases of the sinonasal region (1,6,17). The most common symptoms include facial or toothache, nasal obstruction, and epistaxis (6,17). Paranasal sinus, nasal vestibule and nasopharyngeal cancers should be considered in differential diagnosis in patients over 40 years of age with persistent nasal discharge and epistaxis (6,17,18). Rare symptoms include chronic sinusitis, facial edema, loss of vision, headache, rhinorrhea, and hyposmia, as well as cranial neuropathy such as abnormalities in trigeminal neuralgia and extraocular movements (17,18). Moreover, 40-60% of patients with advanced paranasal sinus cancer have a classic triad of facial asymmetry, palpable or visible tumor in the oral cavity and visible intranasal tumor (17,18).

Symptoms and signs depend on the location of the primary tumor and the extent of the disease. Cancer invasion is very easy because the bone structures between the nasal cavity, sinuses, orbital and cranial cavities are mostly thin (17,19). Locally advanced lesions of the ethmoid sinus may spread through the cribriforme plate into the anterior cranial fossa or the orbit along the lamina papyracea, resulting in the patient's

anosmia or ocular displacement typically upward and / or downward (17,19). Sphenoid sinus tumors can spread directly to the cavernous sinus through cranial nerves III, IV, VI, V1 and V2 along the lateral bone wall and may also invade the middle cranial fossa directly or via the infraorbital nerve. In these patients, diplopia, blurred vision, proptosis, paresthesia may develop due to damage to the trigeminal nerve and trismus may develop in case of pterygoid muscle invasion. In addition, if it spreads into the oral cavity, it may cause painful tooth loss (6,17,18).

5. Staging

It is important to predict the prevalence of the disease in clinical staging (16). Therefore, in all cases, it is recommended to evaluate both primary tumor and possible lend node involvement by inspection, palpation and direct endoscopic examination (16,17). Biopsy for histological typing should be performed following the initial evaluation (17).

Computed tomography and / or magnetic resonance imaging studies are necessary to determine the prevalence of the disease prior to surgical treatment or curative radiotherapy and to distinguish other causes such as infection, secretion plug or granulation tissue (6,17,18). The same evaluation before the treatment plan for relapse is very important, especially in patients undergoing salvage surgery or salvage re-irradiation (17). Unlike other head and neck tumors, staging for paranasal sinus and nasal cavity cancers has not been clearly established. Although not used for staging of lymphoma, mucosal melanomas and sarcomas, Tumor (T), Nod (N), Metastasis (M) [TNM] staging system which is published by American Joint Committee on Cancer (AJCC) in 2017 is preferred for maxillary sinus, ethmoid sinus and nasal cavity cancers. Information on staging is shown in Table 1 and Table 2 (18).

6. Treatment options (Table 3)

When the literature data are reviewed, there is no clear consensus and a randomized study for the optimal treatment of paranasal sinus and nasal cavity cancers, since they are rare tumors and heterogeneous in both histological type and location of the primary tumor (19).

Regardless of nodal involvement, the standard treatment for maxillary and ethmoid sinus adenocarcinomas or squamous cell carcinomas in all T1-T4 tumors is surgical resection, if possible. However, because of the risk of complications such as damage to critical structures such as eyes, brain and cranial nerves, surgical resection is often limited due to primary tumor involvement (7,19-23). Therefore, considering the technological advances for reconstructive approaches and improvements in increasing the quality of life, the decision whether to

undergo surgical treatment in paranasal sinus cancers should be made in a way to include survival, morbidity and functional evaluation (7,19-23).

Local invasion is often common even in early stage lesions in squamous cell carcinoma and adenocarcinomas of the paranasal sinuses and the risk of local recurrence after complete resection is very high in patients who do not receive adjuvant radiation therapy after surgical resection (20,21). Therefore, postoperative radiotherapy should be recommended in the presence of conditions such as poor or positive surgical margin, poorly differentiated histology and perineural invasion, which are considered as poor prognostic factors especially for local recurrence in Stage I and II patients (19,20).

Due to the tendency of early invasion to nearby tissues, it is recommended to evaluate the local spread characteristics of the patients well before resection to determine the most appropriate surgical approach (20-26). The demonstration of orbital involvement is particularly valuable for surgical technique, local recurrence risk and morbidity. Before surgical resection, it is important to evaluate the patients with computed tomography and magnetic resonance imaging and to determine the stage of orbital invasion (26,27). The orbital invasion stage is defined in 3 degrees as follows (27):

- Grade 1 invasion; destruction of the medial orbital wall
- Grade II invasion; invasion of extraconal periorbital adipose tissue
- Grade III invasion; medial rectus, optic nerve, bulbus, eyelid skin invasion

Orbital exenteration is recommended only for patients with grade III orbital invasion (27). For this approach, however, it is often necessary to determine whether the tumor has exceeded the periosteum with frozen sections during surgery (27-31). Orbital exenteration does not have a positive effect on survival in patients with advanced paranasal sinus cancer, but recurrence in orbita is considered to be an important poor prognostic factor (27-29,31). Nevertheless, as in most head and neck cancers, preservation of the orbita by periostal resection is considered an appropriate approach since it can provide a functional eye and provide a comparable survival advantage in case of incomplete periostal invasion (27-29,31). With all these data, orbital exenteration is considered as an appropriate approach in patients with orbital invasion and paranasal sinus malignancies that significantly exceed periorbital (27-31).

Technological advances have enabled the treatment of paranasal sinus tumors with imaging-guided endoscopic resections. In studies, open or endoscopic tumor resection has similar results in terms of obtaining

sufficient surgical margins. In addition to curative treatment, endoscopic sinus surgery may be preferred for palliation of symptoms such as nasal obstruction and epistaxis in paranasal sinus cancers (25,26).

Cervical lymph node metastasis is rare in paranasal sinus and nasal cavity cancers. In a study in which 74 patients with paranasal sinus cancer were followed for more than 25 years, the incidence of cervical lymph node metastasis was 14% at the time of diagnosis or within 5 years of diagnosis (9,32). Neck dissection and subsequent radiation therapy are recommended in all patients with cervical lymph node involvement. However, prophylactic approach with neck dissection or radiotherapy in N0 disease without lymph node metastasis is controversial (9). However; ipsilateral prophylactic neck dissection should be recommended in T3 and T4 cases (9,32,33).

7. Systemic medical treatment

There is no optimal and clear consensus on the use of systemic anti-cancer drugs within the multimodal approach before or after surgery and / or radiotherapy in the treatment of paranasal sinus and nasal cavity cancers. In the literature, it can be added to curative radiation therapy in patients with paranasal sinus and nasal cavity cancer who cannot be resected surgically or can be applied concurrently with adjuvant radiotherapy in patients with poor prognostic features such as positive surgical margin or extracapsular spread after surgical resection (34-40).

In a prospective study by Licitra et al. (41), 49 patients with paranasal sinus cancer, 38 of whom had T3 or T4 tumors, who had no prior treatment and were resectable, have been evaluated. In this study, 19 of the 21 patients who responded after cisplatin-based chemotherapy and 23 of the 28 patients who had no response were treated with surgical and post-operative radiotherapy; the 3-year overall survival rate was reported to be 69% (41). In a study of 39 patients with stage IVB disease who did not undergo surgical resection, 35 patients were treated with curative radiotherapy plus chemotherapy and 4 patients with curative radiotherapy alone. It was reported that 5-year disease-free survival and overall survival rates were approximately 15% for these patients who were followed for over an average 7 years (42).

In a study comparing postoperative adjuvant radiation therapy or concomitant chemo-radiotherapy versus patients who received only concurrent chemo-radiotherapy, the mean progression-free survival was 45 months and the overall survival rate was 65%. It was emphasized that better survival results were achieved in patients who underwent surgery with this study, which included patients with follow-up over an average 6 years (43).

Hanna et al. (43) compared 46 patients who underwent surgery and adjuvant radiotherapy after induction chemotherapy and 22 patients treated with concomitant chemo-radiotherapy. In this study, 67% of all patients had partial or complete response, 9% had stable disease and 24% had progressive disease. The 2-year survival rate of patients who responded to induction chemotherapy was found to be 77%, while this rate was reported to be 36% in patients with progression to induction chemotherapy (44).

In a retrospective study of 179 patients, most of whom had T4N0 disease; induction chemotherapy did not provide significant difference in terms of overall survival results from concomitant high-dose cisplatin and radiotherapy (45).

There is no data in the literature that may differ from other head and neck malignancies in the treatment of patients with metastatic paranasal sinus and nasal cavity cancer (42,46). It is recommended that the anti-cancer drugs to be given in metastatic disease be selected according to the histological type of cancers of the paranasal sinus and nasal cavity. In patients with locally advanced or metastatic squamous cell paranasal sinus and nasal cavity cancer, cisplatin-fluorouracil-cetuximab combination therapy, which is used in metastatic treatment of patients with squamous head and neck cancer other than nasopharyngeal cancer, may be preferred (47).

The prognostic value of PD-L1 positivity in paranasal sinus and nasal cavity cancers is not clear (48). However, it has been reported that promising rates of benefit may be achieved with immune check point inhibitors in metastatic patients (48).

8. Conclusion

When the literature information is reviewed, it is seen that the clinical and treatment characteristics of paranasal sinus and nasal cavity cancers are not clear and that there is no positive development regarding current targeted therapies and immunotherapy options. Because of the rarity of cancers, there is no clear consensus because of the inadequacy of randomized clinical trials based on optimal and standard treatment in terms of surgery, radiation therapy and systemic drug therapies. It may be concluded that new studies are needed for the molecular basis of these cancers, their carcinogenesis characteristics and treatment options.

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Table 1. Definitions in the Tumor (T), Nod (N), Metastasis (M) (TNM) staging system for paranasal sinuses and nasal cavity malignencies designed by the American Joint Committee on Cancer (AJCC) in 2017

Tumor Localization	**T**	**N**	M
Maxillary sinus	Tx Primary tumor could not be evaluated Tis Carcinoma in situ T1 Primary tumor limited to maxillary sinus mucosa without evidence of bone erosion or invasion T2 Primary tumor causing bone erosion or destruction involving extension into the middle nasal m eatus and / or hard palate, excluding extension to the posterior wall of the maxillary sinus and pterygoid plaques T3 Primary tumor invading any of the posterior wall of the maxillary sinus, subcutaneous tissues, orbital floor or lateral wall, pterygoid fossa, ethmoid sinuses T4a Moderately advanced local disease; Primary tumor invading the anterior orbital structures, cheek skin, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses T4b Highly advanced local disease; Primary tumor invading any of the orbital apex, dura, brain, middle cranial fossa, cranial nerves other than the maxillary	Nx Regional lymph node could not be evaluated N0 No regional lymph node involvement N1 Ipsilateral metastasis in a single lymph node with a maximum diameter of cm3 cm and no extranodal spread N2a Ipsilateral metastasis in a single lymph node with a maximum diameter> 3 cm but ancak6 cm and no extranodal spread N2b Metastasis in ipsilateral multiple lymph nodes with a maximum diameter> 6 cm and no extranodal spread N2c Ipsilateral or contralateral lymph node metastases with a maximum diameter> 6 cm and no extranodal spread N3a Lymph node metastasis with the largest diameter> 6 cm and without extranodal spread N3b Metastasis of any lymph node or lymph nodes with clinically	M0 No distant metastasis M1 distant metastasis

	portion of the trigeminal nerve (V2), nasopharynx or clivus	significant extranodal spread	
Ethmoid sinus and nasal cavity	Tx Primary tumor could not be evaluated Tis Carcinoma in situ T1 Primary tumor confined to any background, with or without bone invasion T2 Primary tumor with or without bone invasion involving one of the additional structures within the nasoethmoidal complex or invading two infrastructures in a single site T3 Prier tumor invading the medial wall or base of the orbit, maxillary sinus, palate or cribriforma plate T4a Moderately advanced local disease; Primary tumor invading any of the anterior orbital structures, cheek or nose skin, anterior cranial fossa with minimal spread, pterygoid plates, sphenoid or frontal sinuses T4b Highly advanced local disease; Primary tumor invading any of the orbital apex, dura, brain, middle cranial fossa, cranial nerves other than the maxillary portion of the trigeminal nerve (V2), nasopharynx, or clivus	Nx Regional lymph node could not be evaluated N0 No regional lymph node involvement N1 Ipsilateral metastasis in a single lymph node with a maximum diameter of cm3 cm and no extranodal spread N2a Ipsilateral metastasis in a single lymph node with a maximum diameter> 3 cm but ancak6 cm and no extranodal spread N2b Metastasis in ipsilateral multiple lymph nodes with a maximum diameter> 6 cm and no extranodal spread N2c Ipsilateral or contralateral lymph node metastases with a maximum diameter> 6 cm and no extranodal spread N3a Lymph node metastasis with the largest diameter> 6 cm and without extranodal spread N3b Metastasis of any lymph node or lymph nodes with clinically significant extranodal spread	M0 No distant metastasis M1 distant metastasis

Table 2. Tumor (T), Nod (N), Metastasis (M) (TNM) staging system for paranasal sinuses and nasal cavity malignencies designed by the American Joint Committee on Cancer (AJCC) in 2017

Definitions	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T1, T2, T3	N0 N1	M0 M0
Stage IVA	T4a T1, T2, T3, T4a	N0, N1 N2	M0 M0
Stage IVB	Any T T4b	N3 Any N	M0 M0
Stage IVC	Any T	Any N	M1

Table 3. Treatment recommendations according to tumor localization and disease stage for paranasal sinüses and nasal cavity malignencies

	Stage I	Stage II	Stage III	Stage IV	Recurrence
Maxillary Sinus Cancers	Infrastructure, small, mucosal lesions Primary treatment is surgical resection Post-operative radiotherapy in the presence of close surgical margins, especially in suprastructive tumors	Surgical resection with high-dose, curative pre- or post-operative radiotherapy	Surgical resection with high-dose, curative pre- or post-operative radiotherapy Superfractionated pre- or post-operative radiation therapy is under clinical evaluation	It includes locally advanced lesions and the standard treatment of choice is high-dose definitive radiotherapy for these lesions It has been reported that this treatment option is contraindicated in surgery and is a potential treatment in patients with nasopharyngeal and skull base spread Superfractio	Craniofacial resection with post-operative radiation therapy or post-operative radiotherapy Craniofacial resection after radiation therapy if indicated Chemotherapy should be recommended in case of inadequate treatment after the first two recommendations

				nated radiation therapy, chemotherapy before surgery or curative radiotherapy and adjuvant chemotherapy after surgical treatment or combined-modality treatments are options that can be recommended but are under clinical evaluation	
Ethmoid Sinus Cancers	Tumors with extension usually at the time of diagnosis Non-resectable tumors usually require external radiation therapy alone Good and limited localized tumors can be surgically resected. However, it usually requires a	Tumors with extension usually at the time of diagnosis Non-resectable tumors usually require external radiation therapy alone Good and limited localized tumors can be surgically resected. However, it usually requires a	Surgical resection with craniofacial approach, usually combined with post-operative radiation therapy, is recommended Clinical trials involving new drug combinations with the aim of applying chemotherapy prior to surgery or radiotherapy are under	Surgical resection involving craniofacial approach in combination with pre- or post-operative radiation therapy for those lesions that involve locally advanced lesions and the choice of standard treatment Simultaneous chemo-radiotherapy is a treatment option for non-operable	Radiation therapy or craniofacial resection after limited surgery or both may be recommended Craniofacial resection after radiation therapy Chemotherapy should be recommended in case of inadequate treatment after the first two recommendations

	craniofacial approach including resection of the ethmoid, maxilla and orbit If surgical treatment is performed cosmetically and functionally, adjuvant radiotherapy should be recommended even if surgical margins are safe	craniofacial approach including resection of the ethmoid, maxilla and orbit If surgical treatment is performed cosmetically and functionally, adjuvant radiotherapy should be recommended even if surgical margins are safe	evaluation in advanced tumors and should be considered as recommendations Adjuvant chemotherapy should be recommended after surgical or combined-modality treatments	tumors Adjuvant chemotherapy should be recommended after clinical trials involving new drug combinations, as well as surgical or combined-modality therapies for pre-operative or radiation therapy	Clinical trials involving new chemotherapy agents should be evaluated
Sphenoid Sinus Cancers	Standard treatment offer is primarily radiotherapy as in nasopharyngeal cancers	Standard treatment offer is primarily radiotherapy as in nasopharyngeal cancers Simultaneous chemo-radiotherapy may also be recommended	Standard treatment offer is primarily radiotherapy as in nasopharyngeal cancers Simultaneous chemo-radiotherapy may also be recommended	Standard treatment offer is primarily radiotherapy as in nasopharyngeal cancers Simultaneous chemo-radiotherapy may also be recommended	Standard treatment offer is primarily radiotherapy as in nasopharyngeal cancers In case of inadequate results of this treatment, chemotherapy should be recommended.
Nasal Cavity Cancers	Treatment options for squamous cell carcinoma are either surgical or radiation	Treatment options for squamous cell carcinoma are either surgical or radiation	Standard treatment recommendation is surgery alone, radiotherapy alone,	Standard treatment recommendation is surgery alone, radiotherapy alone,	Nasal cavity squamous cell carcinoma recurrence may be appropriate for the

	therapy because they have similar cure rates Standard treatment is surgery for septum tumors, but for lateral and superior wall tumors, this treatment is radiation therapy, and for septal and lateral wall tumors surgery and adjuvant radiotherapy	therapy because they have similar cure rates Standard treatment is surgery for septum tumors, but for lateral and superior wall tumors, it is either radiation therapy or concurrent chemo-radiotherapy, and septal and lateral wall tumors are surgical and adjuvant radiotherapy	combined surgery and radiation therapy (recommended adjuvant radiation therapy) Concurrent chemo-radiotherapy may be recommended in eligible patients Adjuvant chemotherapy should be recommended after clinical trials involving new drug combinations, as well as surgical or combined-modality therapies for pre-operative or radiation therapy	combined surgery and radiation therapy (recommended adjuvant radiation therapy) Concurrent chemo-radiotherapy may be recommended in eligible patients Adjuvant chemotherapy should be recommended after clinical trials involving new drug combinations, as well as surgical or combined-modality therapies for pre-operative or radiation therapy	treatment of approximately 25% of patients Craniofacial resection is recommended in patients with relapse after radiotherapy, and radiation therapy in patients with recurrence after surgery should be recommended Chemotherapy should be recommended in case of inadequate treatment after the first two recommendations Clinical trials involving new chemotherapy agents should be evaluated