

PANCREATIC CANCER - THE INSIDIOUS DISEASE

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ABSTRACT

Pancreatic cancer is one of the most aggressive forms of malignant disease, often with a long asymptomatic course, early metastases to distant organs and with an extremely poor prognosis.

Here we present the case of a 70-year-old female patient, who was hospitalized in a pulmonology institution with a severe general condition. Due to bilateral lung changes seen on the chest radiograph, she was under suspicion for pneumonia, respiratory insufficiency and had elevated markers of inflammation. On physical examination, paraumbilically on the right, a subcutaneous swelling had been palpated with a harder consistency measuring 7 cm in diameter. She presented an ulcerated umbilicus with a purulent discharge. Nineteen hours after admission, a fatal outcome occurred and the autopsy proved an extended malignant disease (pancreatic ductal adenocarcinoma (aT3N2M1, Stage IV)) with multiple metastases.

It is necessary to adhere to the differential diagnostic algorithm of bilateral lung lesions. Each umbilical nodule should arouse suspicion of the existence of malignant diseases in the abdominal-pelvic region. Therefore, it is of great importance to raise people's awareness about taking control of their health.

Key words: pancreatic carcinoma, Sister Mary Joseph's nodule, bilateral pneumonia

INTRODUCTION

Pancreatic cancer is one of the most aggressive forms of malignant disease with a very poor prognosis (1).

The peak of occurrence of this disease is in the 7th decade of life. It ranks 11th in the incidence of disease and is the 7th leading cause in total mortality among all malignant diseases. It occurs twice as often in men (2).

Additionally, the five-year survival rate is 5%, and the median survival rate of patients with this disease is 17-23 months and 3 months for untreated patients (1). The poor prognosis of this disease is supported by the fact that the annual incidence and mortality are almost equal (3).

The etiology remains unknown, and the most significant variable risk factors for the disease are cigarette consumption, diabetes, obesity and excessive alcohol consumption (4). Immutable risk factors are age, sex, race, family history and inherited genetic syndromes (5).

At the time of the diagnosis, tumors of less than 20% of the patients are resectable and such patients are considered candidates for curative surgical treatment (6). Despite potential curative resection, most patients will experience a relapse of the disease with a 5-year survival rate of 25% (2). The main problem related to this disease is a long asymptomatic course and early metastasis to distant organs. There is still no effective or established early detection method for pancreatic cancer (7). The first onset of symptoms most often occur in an advanced stage of the disease. The prevention and control of metastases is one of the main challenges related to the treatment of this cancer.

The most common site of metastasis is the liver, present in 60-80% of all cases of pancreatic cancer metastasis. Other common sites of metastases are the intra- and retroperitoneal lymph nodes, as well as the peritoneum. Lung metastases are the 4th most common sites of pancreatic cancer metastasis and occur in about 10% of cases (8,9). If the metastatic disease presents itself in an extrahepatic form, i.e. if the disease

initially bypasses the liver and initially presents itself in the lungs, the prognosis of these patients is better (10). Rarer sites of metastasis are bones, kidneys and skin (11). The most common form of skin metastasis is umbilical metastasis, known as Sister Mary Joseph's nodule (12). This type of skin metastasis is not characteristic of pancreatic cancer and it can be seen in numerous intra-abdominal malignancies. However, in 10% of cases this type of metastasis originates from pancreatic cancer (13). Individual cases have been described in the literature that states this cutaneous form of metastasis as the first sign of the disease (14,15).

AIM OF THE STUDY

The case report of a female patient admitted under suspicion of bilateral pneumonia where the autopsy findings indicated disseminated pancreatic malignancy.

CASE PRESENTATION

We present the case of patient R.M., a 70 year old woman, a retired clerk from Novi Sad who was referred to the Institute for Pulmonary diseases of Vojvodina (IPDV) by the general practitioner due to her severe general condition. She presented weakness, malaise and lower back pain in the area of the kidneys. The day before arriving at the IPDV, she was examined by a competent doctor due to her severe general condition. Anamnestically, it is known that it was difficult to move her back ten days ago. Clinical ECOG 3, icteric. When performing lung auscultation, crackles were registered on both sides, more to the left. SaO₂ was 91%, blood count measured leukocytosis (leukocytes 24.9 [4.0-11.0]x10⁹/L), and C reactive protein (CRP) elevated (73.5[<5.0] mg/L). On the chest radiograph, bilateral basal confluent patchy shadows were observed, along with left parahilar shadowing, an elevated left hemidiaphragm, and an enlarged cardiac silhouette (Figure 1). A therapy with third-generation oral antibiotics, diuretics, corticosteroids, and gastroprotective medication was prescribed.

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After reviewing the patient's general condition, laboratory findings, gas exchange and chest X-ray further treatment and diagnosis were needed. Due to bilateral pneumonia and respiratory insufficiency (Figure 1), she was hospitalized at the IPDV.



Figure 1. Chest radiograph on admission.

The patient underwent a gallstone operation 25 years ago. At the time of admission she was under treatment for arterial hypertension and insulin-dependent diabetes. She denied any drug allergy, smoked for 30 years/20 cigarettes per day, did not drink alcohol and had no knowledge of any hereditary diseases.

She was admitted with the aforementioned complaints. On admission to hospital her appetite was preserved and there were no changes in body weight. She was aware, immobile, obese, icteric, afebrile with symptoms of dyspnea and tachycardia, hypertensive with swelling on the lower legs and with a clinical presentation of decompensated heart failure. The lymph nodes were not palpable at predilection sites. She gave the impression of a serious patient.

On auscultation, a weakened respiratory murmur with crackles was registered on both sides of the lungs. Heart action was rhythmic. Tones were clear, audible, without noise.

The abdomen above the level of the chest moved equally and symmetrically with respiration. It was soft to the touch, without defenses and painful sensitivity to superficial and deep palpation. There were no percussive signs of ascites. Peristalsis was audible. The abdominal examination in the paraumbilical region by palpation gave evidence of a subcutaneous swelling to the right with a diameter of about 7 cm with hard consistency, tenderness on palpation, mobile in relation to the base with the overlying skin unchanged. The umbilicus was reddish in color, ulcerated with purulent discharge, which the patient states she has had for a year. The liver and spleen were not palpable on examination.

Vitals at admission: the number of respirations 19/min; SaO₂ 84% with oxygen therapy; body temperature 36.3°C;

systolic pressure 160 mmHg; heart rate 104/min.

Orientation echocardiographic examination: a preserved ejection fraction of the left ventricular myocardium is registered, without signs of right ventricular strain and without pericardial effusion.

Arterial blood gas analysis indicates hypoxemic respiratory failure (PaO₂ 6.81kPa; PaCO₂ 4.17kPa; pH 7.465; SaO₂ 88.1%).

ECG: sinus rhythm, fr. about 100/min. without signs of acute ischemia and myocardial lesion.

An examination of the nasopharyngeal swab ruled out Corona virus SARS-CoV-2 infection.

Complete blood count (CBC): leukocytosis (WBC: 26.8 [4.0-11.0]x10⁹/L), neutrophilia (NEU: 16.04 [2.0-7.6]x10⁹/L); lymphocytosis (LYM: 7.56 [1.0-4.5] x10⁹/L); anemia (RBC: 3.95 [3.8-5.08]x10¹²/L; Hgb: 90 [119.0-157.0] g/L; Hct: 0.286 [0.356-0.47] L/L), thrombocytosis (Plt: 535 [150.0-450.0]x10⁹/L).

In biochemical analyses, the following were elevated: NT-proBNP: 648 [<125.0] pg/mL; glucose: 10.5 [4.1-6.1] mmol/L; AST: 1.76 [<0.53] μkat/L; urea: 17.2 [2.8-8.1] mmol/L; ALT: 1.13 [<0.55] μkat/L; LDH: 16.65 [4.5-7.13] μkat/L; creatinine: 92 [44.0-80.0] μmol/L; bilirubin-total: 135.7 [<21.0] μmol/L; CK-MB: 1.94 [<0.42] μkat/L; bilirubin-direct: 111.4 [<3.4] μmol/L; Y GT: 19.16 [0.1-0.7] μkat/L; CRP: 62.5 [<5.0] mg/L, procalcitonin 1.00 [<0.05] ng/mL, fibrinogen: 5.92 [2.2-5.0] g/L, INR: 1.69 [<1.2], D-dimer: 1599 [<500.0] ng/ml FEU. The following were reduced: sodium: 129 [136.0-145.0] mmol/L; chloride: 91 [98.0-107.0] mmol/L. Potassium and CK were within reference values.

Urine examination: cloudy, yellow, pH5, relative density 1015, protein 1+, glucose, ketone bodies and bilirubin negative, urobilinogen normal, blood 3+, erythrocytes 3-5, leukocytes 5-10, few bacteria. Bacteriological findings of swabs of umbilical ulcerations were without bacterial growth.

Treatment was started with oxygen therapy, parenteral antibiotic therapy (third-generation cephalosporins, respiratory fluoroquinolone), low-molecular-weight heparin, saline infusions, diuretics, antihypertensives, and analgesics as needed, with a urinary catheter placed and diuresis measured.

After 18 hours of hospitalization in the control CBC, leukocytosis and thrombocytosis decreased, anemia less pronounced, control transaminases, nitrogenous substances increased, D dimer, bilirubin decreased. Total proteins: 46.1 [66.0-87.0] g/L; albumins: 22.3 [35.0-52.0] g/L decreased.

Nineteen hours after admission, the patient was found in bed unconscious, without a pulse in the large blood vessels and without measurable vital parameters. Reanimation measures were started immediately, unfortunately without the desired results and the outcome was fatal. Autopsy findings confirmed tumors in the head and body of the pancreas, which histologically corresponded to moderately differentiated (G2) ductal adenocarcinoma with spread to the fat tissue of the

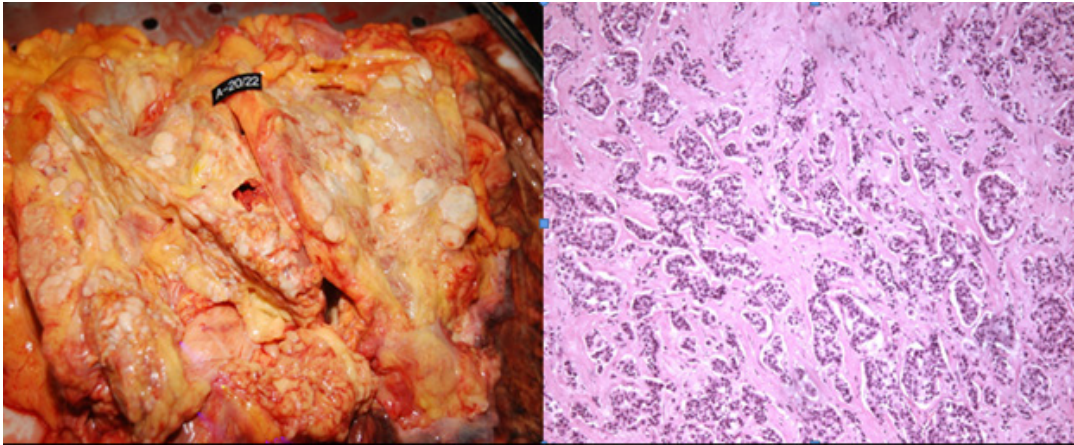


Figure 2. a) Tumor tissue in the head and body of the pancreas; b) Atypical epithelial cells arranged in ducts and immersed in abundant, desmoplastic stroma, H&E x 100.

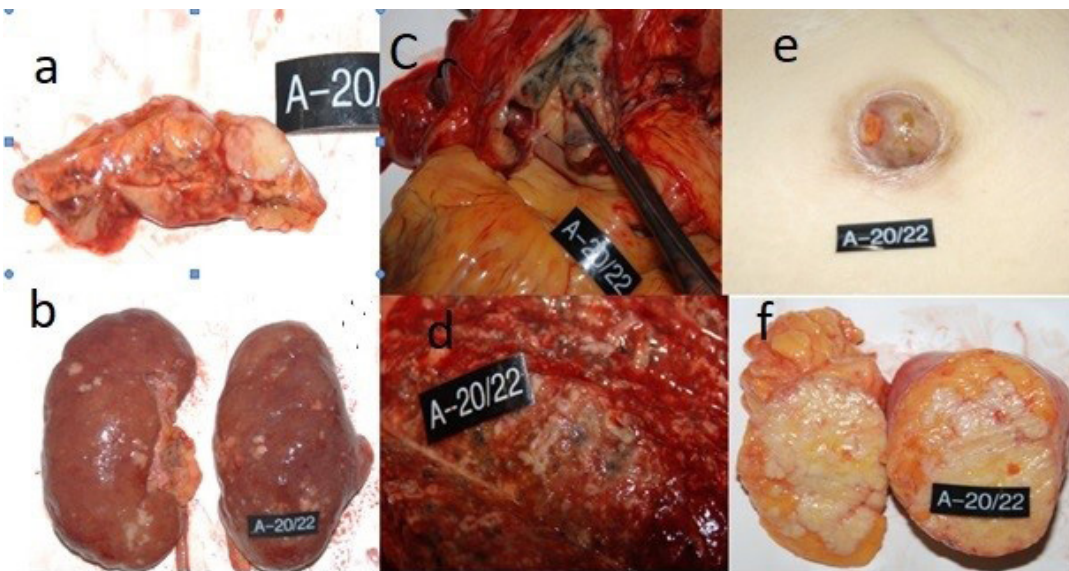


Figure 3. Metastatic deposits: a) adrenal gland; b) bronchopulmonary lymph nodes; c) umbilicus Sister Mary Joseph nodule d) kidney; e) lungs; f) umbilicus – Sister Mary Joseph nodule.

omentum (Figures 2a and 2b). A detailed examination revealed multiple metastatic deposits in various locations: adrenal glands, kidneys, and umbilicus, in the form of a Sister Mary Joseph nodule, both lungs, with carcinoma involving the visceral pleura, and bronchopulmonary lymph nodes (Figures 3 a-f). The patient had an advanced malignant disease, specifically pancreatic ductal adenocarcinoma classified as aT3N2M1, Stage IV. This extensive spread of cancer led to endogenous intoxication, which was the cause of death.

DISCUSSION

The clinical picture of pneumonia in the elderly is a diagnostic problem. The characteristic clinical symptoms and signs of pneumonia may be less prominent, absent or atypically expressed. Often, patients can present with predominantly non-respiratory symptoms, primarily a confused state (16-18). The symptoms described a new-onset acute cough with expectoration, new localized auscultatory findings over the lungs, tachydyspnea, pulse over 100/min, and a fever

lasting >4 days are justified clinical suspicions of the presence of pneumonia (17). Immunocompromised patients can present as afebrile, which was also the case with our patient (19).

Differential diagnosis of bilateral lung changes on the chest radiograph may arouse suspicion of inflammatory lesions of non-specific or specific etiology, malignant, interstitial, stasis lesions or rare diseases (20).

The algorithm for the diagnosis of bilateral lung changes include radiological methods (radiogram, CT, ultrasound of the abdomen), examination of the cardiovascular system, along with a range of biochemical analyses (inflammation markers, insight into possible multi-organ damage, immunological analyses), gas analysis, sputum examinations, as well as pathohistological analysis of the material obtained by invasive pulmonary methods. A cascade of these diagnostic procedures leads to the etiology of bilateral lung changes.

However, the patient's condition was serious and death occurred within the first 24 hours of hospitalization. The short time of hospitalization significantly

limited the diagnostic possibilities that could be used. The autopsy showed that it was an extended malignant disease - adenocarcinoma of the pancreas with multiple metastases.

Pancreatic cancer is an insidious disease and has a long asymptomatic course and early metastasis to distant organs (8).

The most common site of pancreatic cancer metastases is the liver (9), although no liver metastases were found in our patient. Metastases in the lungs occur in about 10% of cases (9,10), as was the case with our patient and it can be said that they were the reason for hospitalization at the pulmonology clinic. Cases of patients with pancreatic cancer whose lung metastases were initially diagnosed as pneumonia (21,22) or interstitial pneumonitis (23) are described in the literature.

The most common form of skin metastasis is umbilical metastasis, known as Sister Mary Joseph's nodule (13). It is a rare but significant clinical finding that indicates advanced malignant disease and a poor prognosis. Sister Mary Joseph's nodule was first described in the literature in 1864, named after Sister Mary Joseph (1856-1939), who was a surgical assistant to Dr. William James Mayo, who first noticed the connection between abdominopelvic malignancies and metastatic umbilical nodules. The Sister Mary Joseph's nodule occurs rarely, in about 1-3% of abdominopelvic malignancies. It is most often associated with primary neoplasms of the gastrointestinal tract (35-65%) and genitourinary tract (12-35%). In men, the change mentioned is most often of gastrointestinal tract malignancy, and in women of gynecological malignancy.

Other malignancies associated with its occurrence are tumors of the lung, pancreas, liver, gall bladder, breast, kidney, penis, prostate, testicles, and lymphomas. In 30% of cases, it is impossible to detect the primary origin of the disease (24).

The described mechanisms of the formation of the mentioned nodules are directly related to the spread of the tumor in the umbilicus, by lymphogenous or hematogenous metastasis. It is clinically presented as an umbilical or paraumbilical nodule, with a hard consistency, variable diameter, often painful to the touch, with pus secretion, which is often the only complaint. The differential diagnosis of an umbilical nodule includes primary umbilical neoplasm, umbilical hernia, umbilical endometriosis, keloid, pyoderma, foreign body (25).

Patients with the present sign have a poor prognosis with an average survival of 11 months (26). Most of the case reports on the subject of the umbilical nodule state the clinical sign as the primary manifestation of malignant disease (27-29). In our case, the patient noticed a change in the navel a year ago, but did not contact the doctor.

Also, the patient was 70 years old, which is in agreement with the literature data on the peak incidence of pancreatic cancer (2). The age of onset is not a sufficiently specific or sensitive factor that can lead to the diagnosis of this malignant disease, especially when

the limit and peak of the disease tend to shift towards the younger population. Regarding the risk factors for pancreatic cancer, the patient was a long-term smoker, had diabetes, and was obese.

This case confirms that pancreatic cancer is an insidious disease, asymptomatic for a very long time, which is the main reason our patient asked and received medical help late. Although she had a purulent discharge from her navel for almost a year, she paid no attention. It was only weakness, lassitude, endogenous intoxication, and respiratory insufficiency as a consequence of bilateral lung metastases that brought her to a health facility. Considering the radiological findings and elevated markers of inflammation, upon admission it was understood as severe bilateral pneumonia, of course bearing in mind the differential diagnosis of bilateral lung lesions. Unfortunately, the fatal outcome occurs less than 24 hours after hospitalization. The autopsy report finally determined that the cause of death was endogenous intoxication caused by an extended malignant disease with multiple metastases.

CONCLUSION

It is necessary to adhere to the differential diagnostic algorithm of bilateral lung lesions. Each umbilical nodule should arouse suspicion of the existence of malignant diseases in the abdominal-pelvic region. Therefore, it is of great importance to raise people's awareness about taking control of their health.

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