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IM - CASE RECORD

Fever, edema, and shortness of breath: the Scrhödinger's cat paradox displayed on pericardium

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Case presentation

In June 2017, a 50-year-old woman was admitted to our ward with fever, edema of the lower limbs, jugular turgor, fatigue, tachycardia, and dyspnea of 2 weeks duration. In the Emergency Department (ED), the patient was febrile (38 °C); the physical examination showed signs of right heart failure with tachycardia (110 bpm), hypotension (90/60 mmHg), and peripheral oxygen saturation 98%. A chest X-ray study revealed a left pleural effusion; blood examinations demonstrated increased values of C-reactive protein (CRP) 8.23 mg/dl (normal values < 0.5) and international normalized ratio (INR) was 1.44; echocardiogram showed minimum anterior pericardial effusion. The ECG was normal apart from nonspecific abnormalities of ST-T waves.

Her medical history was significant for locally invasive uterine cervical squamous cell carcinoma (SCC) discovered in 2015, treated with chemotherapy and radiotherapy. Subsequent follow-up at 2 years (gynaecologic visit in April 2017) was negative for recurrence; the only altered examination was the SCC marker, elevated to 8 µg/l (previous 1.7 µg/dl). She was hospitalized 3 months prior for pleuropericarditis of unknown origin. During that hospitalization, she underwent echocardiography and cardiac magnetic resonance (MRI) that revealed a partially organized diffuse pericardial effusion with hematic appearance. Several other investigations were performed including ECG, thorax computed tomography (CT) scan with contrast medium targeted to pulmonary embolism, thoracentesis, blood culture, viral and bacterial serology, quantiferon-tuberculosis (quantiferon-TB), immunologic screening, and abdomen and thyroid ultrasound, without evidence of other acute alterations except for bilateral pleural effusions. She started a therapy with ibuprofen, colchicine, and bisoprolol, and she was discharged in April 2017.

Dr. Gesu and Dr. Costantino (Internists)

Considering the main symptoms of the patient (fever and signs of right heart failure), the recent pericarditis, and the medical history of neoplastic disease, the more likely diagnoses were subacute/relapsing infectious pericardial disease (with particular relevance of the mycobacterial hypothesis), neoplastic pericarditis, autoimmune disease, or another unknown infection. For a better evaluation, thorax and abdomen CT scans were performed. Moreover, to complete the diagnostic picture, cardiac MRI and total body positron emission tomography (PET) were then requested.

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Dr. Maria Carmela Andrisani, Dr. Valentina Vespro, and Dr. Enrico Garanzini (Radiologists)

The chest CT scan showed a diffuse irregular thickening of the pericardial layers, with several nodular lesions diffusely spread around the pericardium, the bigger of them (more than 4 cm in maximum diameter) along the right atrial and ventricular walls. These lesions showed heterogeneous contrast enhancement, with areas of central necrosis/colliquation. Furthermore, there was a gas collection (diameter of 4 cm) bounded by the pericardial layers adjacent to the pulmonary artery. A systemic venous dilatation of the inferior vena cava and suprahepatic veins with hepatomegaly were also present, suggesting pericardial constriction. Moreover, a thrombosis of the left upper pulmonary vein was present. In the left upper lobe, pulmonary consolidations with irregular thickening of interlobular septa were present, a finding which was interpreted as possible carcinomatous lymphangitis or pneumonia.

This picture was initially interpreted as several pericardial metastatic lesions, with possible infectious complication (abscesses). The alternative hypothesis was pericarditis with pericardial abscesses.

To better differentiate the malignant pericardial disease from inflammatory pericarditis and to detect signs of pericardial constriction, a cardiac MRI was performed. In this clinical situation, MRI is considered to have great potential utility because information regarding pericardial-cardiac morphology and tissue characteristics can be merged with functional hemodynamic information [13, 14].

The MRI showed the presence of pericardial round-shaped confluent formations, the larger around the right heart chambers. Such lesions were hyperintense in the T2-weighed and hypointense in the T1-weighed images. After administration of intravenous contrast medium, there was no enhancement of the central portion but enhancement of the walls, suggesting infected fluid collections. Pericardial leaflets appeared thickened up to 4 mm. In the delayed enhancement and short-tau inversion-recovery (STIR) sequences, a widespread hyperintensity of pericardial leaflets was observed. In the real-time film sequences, the "flattening" of the interventricular septum was noted in maximum inspiration, suggesting pericardial constriction of the right heart chambers.

The MRI findings were then suggestive for subacute pericarditis complicated with abscesses and signs of constrictive pericarditis.

Finally, a total body CT-PET was performed, demonstrating diffuse pericardial (standard uptake value—SUV—max 11.7), mediastinal, and upper left lung lobe

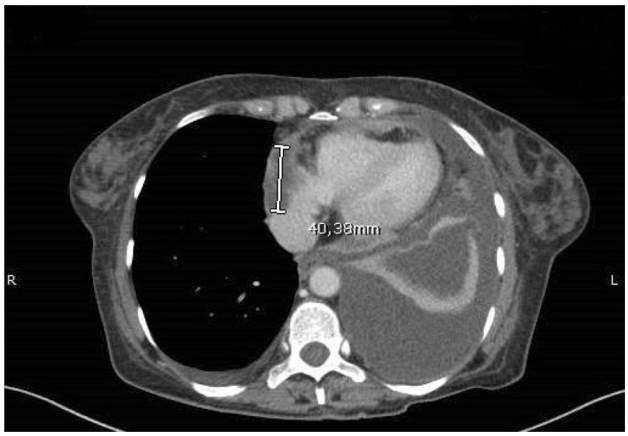

Fig. 1 The CT scan (mediastinal window level) shows nodular lesions of the pericardium, the bigger of them (more than 4 cm in maximum diameter) along the right atrial and ventricular walls. These lesions showed heterogeneous contrast enhancement, with areas of central hypodensity because of necrosis/colliquation

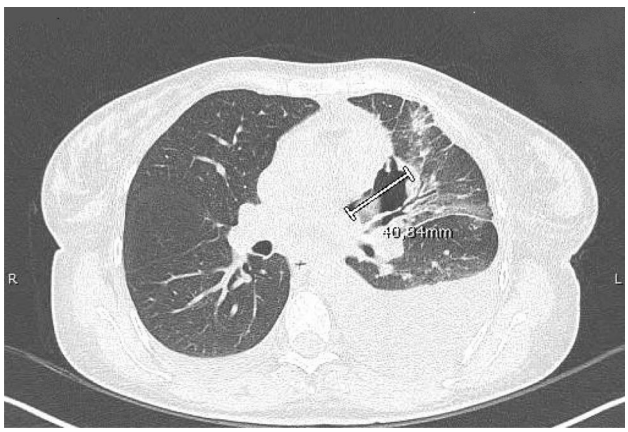

Fig. 2 The CT scan (lung window level) shows, adjacent to the right pulmonary artery and to the lingular bronchus, a gas collection (diameter of 4 cm) bounded by the pericardial layers

(SUVmax 4.6) hypermetabolic tissue, that could be the expression of both neoplasia and infectious disease.

On one hand, the CT scans revealed necrotic/colliquative pericardial lesions, thrombosis of the left upper pulmonary vein, intrapericardial gas collection, and new pulmonary left apical consolidations, findings more suggestive in a patient with previous history of neoplasia of the uterine cervix, for metastatic disease (from the previous cancer or from a new one) rather than for pericarditis. On the other hand, the MRI features appeared typical for the evolution of a previous acute pericarditis with constrictive pericarditis (Figs. 1, 2, 3, 4).

A previous CT of the chest, performed 3 months earlier in another hospital, was available and reviewed by radiologists specialized in chest imaging. In the previous CT scan, the

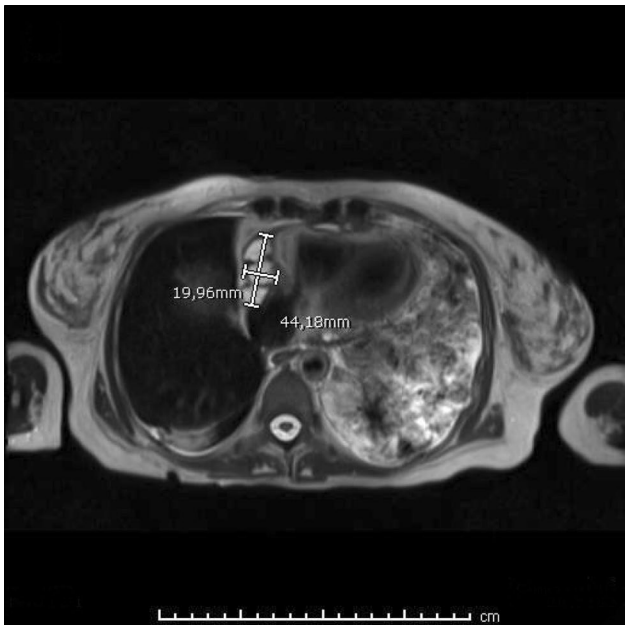

Fig. 3 T2-weighed image without intravenous contrast show hyperintense pericardial lesion suggestive for fluid collection

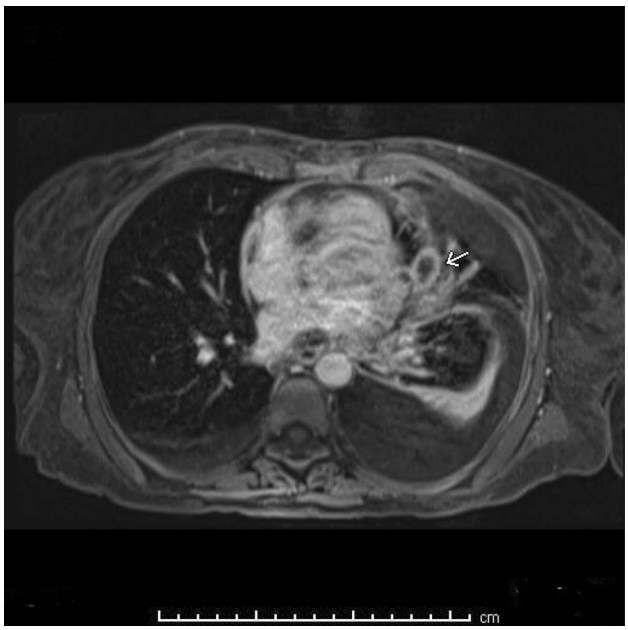

Fig. 4 On T1-weighed image with intravenous contrast, the pericardial lesions show ring enhancement, finding interpreted as infected lesions

pericardial thickening and the air collection were already present, and the gas collection was attributed to a broncomediastinal fistula; the left lung consolidations were not present.

In conclusion, a meeting of all the radiologists involved in the case took place. The radiologists were in agreement—even not being able to completely exclude the neoplastic origin of the clinical picture—considering the bronchial fistula at the origin of the pericardial inflammation with subsequent infectious complications.

Considering the possible presence of mediastinal abscesses, an antibiotic therapy with imipenem and vancomycin was started. The patient was also given Ivabradine 5 mg bis in die and low dose of intravenous diuretics.

The clinical case was presented to thoracic surgeon, to collect an opinion about the patient and plan bronchoscopy and bronchoalveolar lavage, and furthermore, the case was discussed with the infectious disease specialist.

Dr. Ilaria Righi (Thoracic Surgeon)

Because of hypotension and the fragile status of the patient, any invasive procedure had to be evaluated carefully. The target tissues for the diagnosis were in different sites of the thorax, which could be reached with different diagnostic procedures of different grades of invasiveness. The PET showed uptake in the pericardial nodules, in the left hilum and mediastinal pleura. To obtain a diagnosis on these tissues, the indication was to perform a left thoracoscopy to make pericardial and pleural biopsy, that in our opinion were the best way to confirm or exclude malignancy. However, the clinical conditions of the patients were too delicate to perform such kind of surgery without life-threatening risks. Other sites of uptake were localized into the left upper lung lobe, probable site of broncho pleural fistula at CT images. To have information about the lung, the best choice would have been bronchoscopy with bronchoalveolar lavage, to obtain microbiological cultures and to detect the suspected fistula, but with low sensitivity to find malignancies. Moreover, such kind of intervention would have been performed when the clinical condition of the patient would be less fragile.

Dr. Stefania Piconi (Infectious Diseases Specialist)

CT scan, cardiac RMN, and CT-PET were not able to make a distinction between infectious and neoplastic lesion. Nevertheless, the suspected presence of an endobronchial fistula made us start an empirical antibiotic therapy. A thoracentesis was performed, with no evidence of bacteria, fungi, or mycobacterium tuberculosis (microscopic, polymerase chain reaction analysis, and cultural test). To evaluate other possible infectious causes of effusive/constrictive pericarditis, several tests such as blood cultures, blood quantiferon-TB, aspergillus galactomannan and *Cryptococcus neoformans* blood antigen, *Histoplasma capsulatum*, *Echinococcus*, enterovirus, and aspergillus antibodies, and CMV, EBV,

HHV6, HHV8, adenovirus, and parvovirus-B19 plasmatic DNA were performed. All these analyses were negative.

Over the next 2 weeks, the patient improved from a clinical point of view. No more significant hypotension, tachycardia, and fever were present. Blood tests revealed that CRP had slightly reduced.

Considering the absence of a diagnosis, the age of the patient and her clinical status, a heart surgery evaluation was requested to evaluate the possibility of a pericardiectomy.

The surgeon was worried about the possible malignant origin of the pericardial effusion and the consequences of such kind of surgical intervention. He wanted to be sure about the infectious origin of the pericardial effusion before performing surgery. He asked for a bronchoscopy and transthoracic needle biopsy. The improved clinical status of the patient allowed the performance of these procedures, and both were negative for malignant cells. The bronchial alveolar lavage was also negative for bacterial, virus, galactomannan antigen, and mycobacteria.

The surgeon then asked for cardiac catheterization and coronary angiography, which revealed severe constrictive pericarditis.

He was still not sure about the origin of the effusion, and, to exclude a neoplastic disease, he asked for pericardial biopsy during thoracoscopy.

Dr. Gesu and Dr. Costantino

The diagnosis of the patient was still uncertain. There was the possibility of a neoplastic origin as well as an infectious disease. Even if in the neoplastic hypothesis, the prognosis would have been very poor and there would not have been any satisfying therapeutic option—and in that case, the surgical risk of pericardiectomy would have been very high with probable worsening of the quality of life—on the other hand, in the infectious hypothesis, the surgical procedure would have implied more chances of survival and more probabilities of good symptomatic relief before severe constriction and myocardial atrophy occurred.

Even if pericardial biopsy would have provided a final diagnosis with less surgical risks and impact on quality of life, it was a surgical procedure in general anesthesia, and if the infectious hypothesis was confirmed this compromised patient would have to undergo two surgical interventions in general anesthesia in a few days.

At that point, we were in a state of paradox similar to that of Schrödinger's cat. Schrödinger's cat is an ideal experiment that consisted of enclosing a cat in a box with a deadly trap that could be spontaneously triggered at an unpredictable moment. Opening the box would activate the trap killing the cat. Not opening the box, therefore, makes it impossible to know if the trap is activated and if the cat is alive or dead. It is, therefore, necessary to suppose the cat being simultaneously alive and dead. Likewise, in our situation, it was impossible to know whether the origin of the symptoms was neoplastic or infectious without opening the chest of the patient. Until then, etiology should be considered simultaneously infectious and neoplastic. But opening the chest of the patient was very difficult for clinical implications.

Considering the cost-effectiveness ratio, we concluded that it was indicated to perform pericardiectomy.

In addition to the difficult clinical decision at that point, there was the problem of a different opinion among the patient's care providers (us) and those who would perform the surgical intervention. This opens up a major ethical problem for cases where the opinion of the care provider, who daily cares about the patient's responsibility, disagrees with that of the consultant, who should practically execute a procedure.

In the end, we decided to deal with the paradox requesting for a cardio-surgical second opinion.

Meanwhile, the conditions of the patient returned to the clinical situation of the admission, and then continued to get worse. She was no more febrile, but CRP value was still elevated. We needed to use increasing doses of Ivabradine and diuretics for the right heart failure, but after slight initial improvement, she relapsed becoming hypotensive and tachycardic, and we had to stop these medications. Edema worsened and, at the same time, blood examinations showed a slow progressive increasing in liver enzymes and INR values, consistent with hepatic hypoperfusion, and the serum lactate started to rise.

Dr. Guido Gelpi (Cardiac Surgeon)

A second opinion was asked for a 50-year-old woman with signs and symptoms of constrictive pericarditis of uncertain origin. After a complete re-evaluation of the clinical history of the patient, the radiological examinations, and the worsening of the clinical condition, the patient was transferred to the Cardiovascular Surgery Department. A new echocardiogram confirmed the suspect of constrictive pericarditis, and a new left thoracentesis drained 1500 cc of clear pleural effusion. Despite the best medical therapy and the pleural drainage, the clinical condition of the patient continued to get worse with clear signs of low cardiac output syndrome. An urgent surgical intervention was judged, the only diagnostic and possible therapeutic option. After opening the sternum and partial opening of the pericardium, a solid mass covering the entire heart was revealed. A biopsy of the solid mass was performed during surgery. The malignant nature and the extension of the neoplastic mass incorporating the entire heart induced the decision to not proceed further with any surgical attempt. The patient was never awakened, and

Table 1 Aetiologies of pericarditis (modified from 2)

Infectious causes
Viral (common): enteroviruses, herpesviruses, adenoviruses, parvovirus B19
Bacterial: *Mycobacterium tuberculosis*, *Coxiella burnetii*, *Borrelia burgdorferi*
Rarely: *Pneumococcus* spp, *Meningococcus* spp, *Gonococcus* spp, *Streptococcus* spp, *Staphylococcus* spp, *Haemophilus* spp, *Chlamydia* spp, *Mycoplasma* spp, *Legionella* spp, *Leptospira* spp, *Listeria* spp, *Providencia stuartii*
Fungal (very rare): *Histoplasma* spp, *Aspergillus* spp, *Blastomyces* spp, *Candida* spp
Parasitic (very rare): *Echinococcus* spp, *Toxoplasma* spp
Non infectious causes
Autoimmune (common): systemic autoimmune and autoinflammatory diseases (lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma), systemic vasculitides, sarcoidosis, familial Mediterranean fever, inflammatory bowel disease, Still disease
Neoplastic: primary tumors, secondary metastatic tumors (lung and breast cancer, lymphoma)
Metabolic: uraemia, myxedema, anorexia nervosa
Traumatica and iatrogenic: Early onset (rare): Direct injury (penetrating thoracic injury, esophageal perforation) Indirect injury (non-penetrating thoracic injury, radiation injury) Delayed onset: pericardial injury syndromes such as postmyocardial infarction syndrome, postpericardiotomy syndrome, posttraumatic, including forms after iatrogenic trauma
Drug-related (rare): Lupus-like syndrome; antineoplastic drugs; penicillins as hypersensitivity pericarditis with eosinophilia; amiodarone, methysergide, mesalazine, clozapine, minoxidil, dantrolene, practolol, phenylbutazone, thiazides, streptomycin, thiouracils, streptokinase, p-aminosalicylic acid, sulfadrugs, cyclosporine, bromocriptine, several vaccines, GM-CSF, anti-TNF agents
Other (common): amyloidosis, aortic dissection, pulmonary arterial hypertension and chronic heart failure.
Other (uncommon): congenital partial and complete absence of the pericardium

due to the progressive low cardiac output syndrome, she died on the second postoperative day.

Discussion and comment

Our patient had an extremely rare clinical condition. Only 18 cases of cardiac (pericardial or intracardiac) metastasis of uterine cervical cancer diagnosed antemortem were reported in the literature until 2016 [1, 9], while the incidence of cardiac metastasis of uterine cervix tumors from autopsy studies is 3–4% [5]. On the other hand, metastatic involvement of the heart is quite common in patients dying of cancer (8%) [6]. Cardiac metastases of cervical squamous cell carcinomas are more probable in the first 2 years, after the completion of the treatment. In this period, patients with these kinds of neoplasms should be strictly monitored [1, 3, 10]. Mean survival is not clearly defined, from case reports it varies from 4 to 6 weeks to few months, with a poor quality of life [1, 9, 12]. A longer survival was reported only for very few patients. Treatment of pericardial metastasis has not yet been standardized, particularly with no clear evidence of benefits from an aggressive therapy. Possible treatments include metastases excision, systemic chemotherapy, and radiotherapy. Treatment should be evaluated case-by-case based on the clinical conditions of the patient [1].

The differential diagnoses of pericardial effusion include infectious, neoplastic, autoimmune diseases, and others (see Table 1). Laboratory or radiologic tests provide diagnostic support; however, pericardiocentesis or pericardial biopsy is needed to obtain a specific diagnosis [2, 7].

Pericardiectomy is the only definitive therapy for constrictive pericarditis. Based on the literature, it provides a complete regression of symptoms in 70% of patients affected. Pericardiectomy is an insidious surgery, and it is difficult to decide the right time to perform the surgical operation: if too early in the disease and with a poorly symptomatic patient, surgical risks potentially outweigh the benefits. On the other hand, if carried out too late, there are no benefits from surgical intervention, and there is a worse prognosis due to myocardial atrophy and systemic impairment. Intraoperative mortality is reported to be 8–12%, and after the surgery, long-term survival at 5 years be 80% [4, 8, 11].

The last problem highlighted by this case is that of disagreement between a care provider and a consultant. Although the clinical responsibility of the patient falls on the physician who daily visits and follows the patient, in this case the internists are not able to perform all the technical procedures and they think are advisable. If the consultant, who is technically able to perform such procedures, is in disagreement, then an ethical problem raises whether at a certain point the consultant assumes the responsibility for the patient or whether it remains on the physician who at that moment is in charge of the patient but cannot practically proceed. There is currently no coded method to overcome

this situation, which in our case was similar to a paradox. In our case, therefore, we decided to face the impasse, to be able to handle the treatment that in this complex situation seemed to us the best available option at that time, requiring a second opinion. At present, this remains an open question concerning the areas of clinical responsibility, ethics, and professional etiquette.

Compliance with ethical standards

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

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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