

Cutaneous Nodules - A Challenging Presenting Sign in Breast Neoplasm**Mihalcea R, Radu F, Bordea A, Patru R, Manolache R, Popa I, Salcianu I, Spataru D and Savulescu-Fiedler I****Coltea Clinical Hospital, Romania****Corresponding Author**

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Dr Mihalcea (Internal Medicine): A 77-year-old woman was admitted to the hospital because of dyspnea at rest, fatigability, unproductive cough (debuted 6 months prior to admission, with no improvement from common cough medication), and the onset, reportedly during the previous two months, of painful, erythematous, hard nodules distributed diffusely all over her body. She had a history of rheumatic heart disease, with severe mitral-valve stenosis, atrial fibrillation, and heart failure with reduced ejection fraction. Two months earlier she was admitted for a routine check-up at the Cardiology Ward of the hospital where she was being monitored for her cardiovascular pathology, and no nodules were reported.

Forty years earlier she had undergone open mitral-valve commissurotomy for severe rheumatic mitral-valve stenosis. Seven years earlier, she had undergone mechanical mitral-valve replacement (ST Jude prosthesis) for severe mitral-valve regurgitation developed during the decades following the commissurotomy intervention, with the initiation of long-term anticoagulation vitamin K antagonist (Acenocumarol). In the following years she developed severe mitral-prosthesis stenosis with secondary left atrial enlargement, pulmonary hypertension, right ventricular dilatation, severe tricuspid-valve regurgitation and left ventricular hypokinesia. Her cardiovascular pathology also included major right-bundle block, grade III ESC/ESH arterial hypertension, hypercholesterolemia and chronic kidney disease stage II, with a creatinine level of 0.96 mg per deciliter (84.88

μmol per liter; reference range, 0.55 to 1.02 mg per deciliter [48.63 to 90.19 μmol per liter]) and an estimated glomerular filtration rate (GFR) of 57 ml per minute per 1.73m² of body-surface area (reference range, >60) according to the Modification of Diet in Renal Disease (MDRD) formula.

On examination, the temperature was 37,1oC, the blood pressure 120/60 mmHg, heart rate 80 beats per minute, the respiratory rate 16 breaths per minute and the oxygen saturation 92% while the patient was breathing ambient air. She presented with dyspnea at rest, thus classifying her as New York Heart Association (NYHA) Functional Class IV. The patient was slightly overweight, with the weight of 66 kg, and the body-mass index (BMI) 26.6 kg/sqm. She was awake, aware of her surroundings and cooperant. She had excess adipose tissue on her abdomen and multiple hard, erythematous and painful nodules, the largest with the diameter of approximately 5 cm, diffusely distributed on her anterior and posterior thorax, right scapular region, upper limbs and left thigh (Figure 1). Breast examination revealed extensive post-combustion keloid scars on her anterior thorax and a hard, mobile, non-painful nodule in the right breast. There were bilateral and symmetrical lower leg edema, with no signs of superficial or profound venous thrombosis. Crackles were present in both lung fields. The cardiac rhythm was irregular, with audible prosthesis sounds and diastolic murmur in the tricuspid point; both jugular veins were distended. Bowel sounds were present and the abdomen was distended by excess adipose tissue, soft, and nontender on palpation. Profound abdominal palpation revealed an enlarged liver.

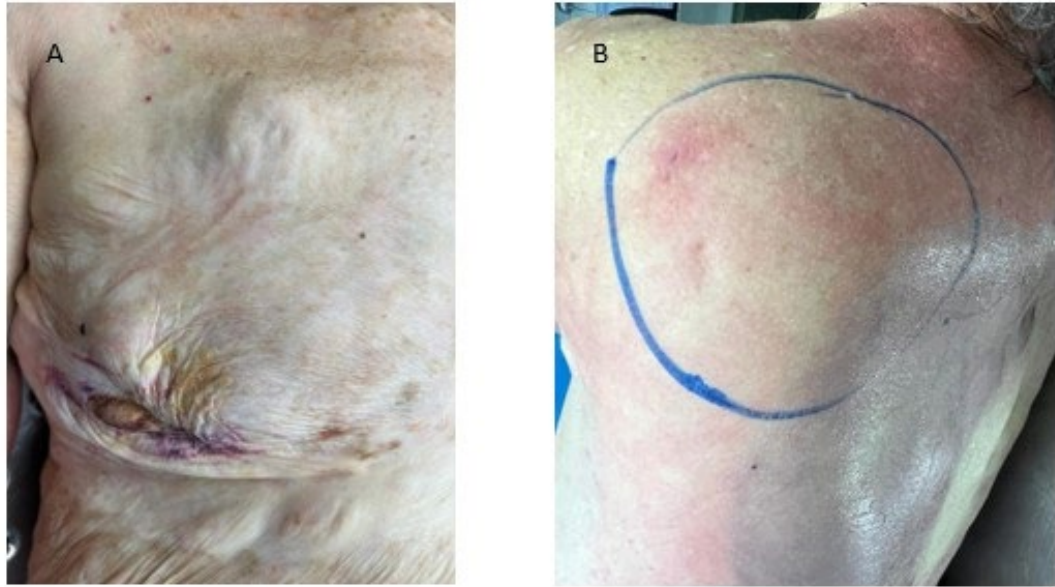


Figure 1: Cutaneous Nodules

Anterior and posterior thoracic nodules (Panels A and B, respectively), some of them erythematous. Panel A also shows extensive post-combustion keloid scars on the anterior thorax.

The complete blood count revealed mild leukocytosis with neutrophilia and a lowered erythrocyte count, with normal levels of hemoglobin. Initial biochemical tests suggested normal liver and pancreatic function, but showed an important increase in lactate dehydrogenase (LDH) levels and mildly elevated total bilirubin in the presence of normal levels of direct bilirubin, indicative of hemolysis. Mild inflammatory syndrome was present, consisting of elevated levels of C-reactive protein, fibrinogen, D-dimer and an increased erythrocyte sedimentation rate (ESR). Other laboratory results of note include increased creatine phosphokinase-MB (CK-MB) with normal creatine phosphokinase (CK) levels. Further blood tests revealed normal levels of thyroid (TSH, thyroid stimulating hormone; FT4, free thyroxine) and parathyroid (PTH, parathyroid hormone) hormones.

We also mention highly elevated blood levels of N-terminal prohormone of brain natriuretic peptide (NT-ProBNP), indicative of her advanced cardiovascular pathology, and altered blood coagulation results, with an increased prothrombin time evaluated by international normalized ratio (INR) and activated partial thromboplastin time (aPTT), suggesting Acenocumarin overdose. Urinalysis showed the presence of erythrocytes, ketones and proteins (reference range, negative). The urine culture returned less than 10000 colony forming units (CFU, reference range <10000). Immunological blood tests revealed an increase in beta-2 microglobulin and normal levels of immunoglobulins A, G and M, and immunoglobulin light chains. In the presence of normal blood albumin and total protein levels, blood protein electrophoresis revealed slightly elevated levels of Alpha-1 globulins. A summary of the most important laboratory tests is shown in Table 1.

Variable	Reference Range, Adults	On Presentation
Sodium (mmol/liter)	137-145	139
Potassium (mmol/liter)	3.6-5	5.1
Glucose (mg/dl)	74-106	103
ESR (mm/1 h)	4-13	34
C-reactive protein (mg/dl)	0-0.32	5.4
CK-MB (U/L)	0.2-16	19
LDH (U/L)	120-246	806
Total bilirubin (mg/dl)	0.2-1.3	1.48
Creatinine (mg/dl)	0.55-1.02	0.96
INR	0.89-1.08	5.95

Fibrinogen (mg/dl)	150-400	603
NT-ProBNP (pg./ml)	0-300	2340

Table 1: Laboratory Data

The electrocardiogram (ECG) showed no signs of newly installed arrhythmia or acute myocardial infarction.

Chest radiography (Figure 2) revealed wires associated with median sternotomy and evidence of mitral-valve repairs. There was evidence of global cardiomegaly and mild interstitial pulmonary edema. Diffuse demineralisation lesions were observed on bone radiographies.

Echocardiogram examination reveals mechanical mitral-valve prosthesis with a mean diastolic gradient measuring 4.5 mmHg, dilated left atrium (160 ml), dilated left ventricle (5.6 cm),

tricuspidian regurgitation with vena contracta 2 cm, peak right ventricular-right atrial diastolic gradient 32 mmHg, mean diastolic gradient 4 mmHg and peak regurgitation velocity 8 cm/s, global hypokinesia with paradoxical septal motion and an estimated ejection fraction 35%. Abdominal ultrasound reveals dilated inferior vena cava with no inspiratory variation, hepatic congestion and systolic hepatic vein flow reversal.

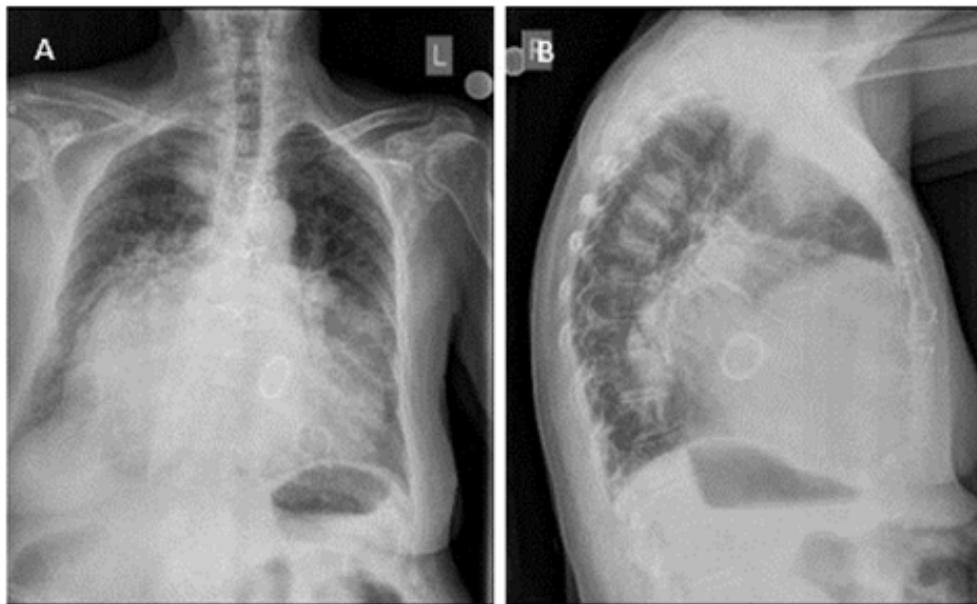


Figure 2: Chest Radiographs

Posteroanterior and lateral chest radiographs (Panels A and B, respectively) show evidence of global cardiomegaly, interstitial lung edema and mitral-valve repair.

We effectuated a native-phase only Computer Tomography (CT) due to the patient's history of allergic reactions. Head examination revealed no pathological findings, except for diffuse cortical atrophy. The examination of the thorax segment showed global cardiomegaly, mechanical mitral-valve prosthesis, subpleural nodules in both lungs (the largest being 1.3 cm in diameter), bilateral parenchymal bands suggestive of pulmonary fibrosis, especially in the lower segments and multiple mediastinal enlarged lymph nodes, the largest being 2.8/1.5 cm in diameter. The examination of the abdominal segment revealed hypodense nodules in the both liver lobes (the largest 2.2 cm in diameter), enlarged inferior vena cava and suprahepatic veins, bilateral suprarenal nodules (1.8/0.9 cm in diameter, right side; 1.3/0.9 cm in diameter, left side), enlarged lymph nodes adjacent to the lumbar segment of

the aorta (2.8 cm in diameter), between the aorta and the inferior vena cava (1.6 cm in diameter) and adjacent to both common iliac arteries (the largest 1.8 cm in diameter), and a mesenteric lymphadenopathy mass, 6 cm in diameter, with compressive effect on the aorta and the inferior vena cava. The examination also showed multiple nodules infiltrating the epidermis, subcutaneous adipose tissue and muscular tissue (musculuspectoralis major, musculuslatissimusdorsi and musculus serratus anterior). The nodules appear to have a nonhomogeneous internal structure, with smooth outlines. We also describe a nodule in the upper outer quadrant of the right breast, presenting spiculation, 2.2/1.5 cm in diameter (Figure:3). I recommend completing the investigations with bone scintigraphy.

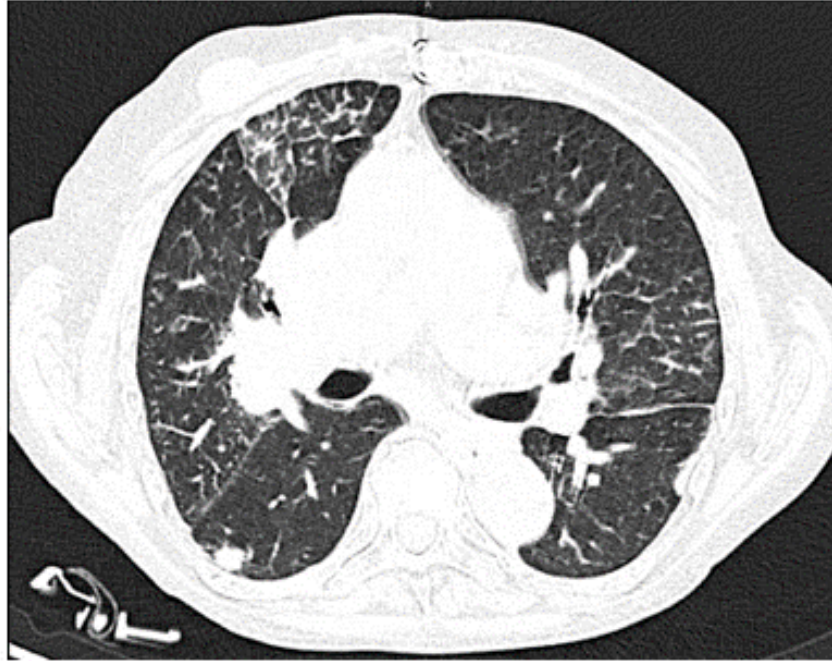


Figure 3: Computer Tomography (CT) Chest Segment

Chest segment CT shows cardiomegaly, parenchymal bands, subpleural nodules, and nodule in the right breast. The patient was admitted to the hospital, and a diagnostic test was performed.

2. Case Report

2.1. Differential Diagnosis

This 77-year-old woman came to the Emergency Department for dyspnea at rest and fatigability, symptomatology suggestive of acutely decompensated congestive heart failure, considering her known medical history. Unrelated to her cardiovascular-centered clinical presentation were the cutaneous nodules, with inflammatory elements, which the patient noted during the two months following her last medical check-up. It is unclear whether the nodules appeared in such a short time, or whether they were missed during previous medical examinations. While the clinical examination revealed a breast nodule with features suggesting malignancy, accompanied by axillary adenomegaly, it must be investigated whether it shares an etiology with the cutaneous nodules, or whether it is a separate lesion, and possibly the cause of the cutaneous manifestations.

After immediate management of her acute cardio-vascular pathology, we continued the diagnostic tests for the etiology of the nodules.

We are now facing a patient with multiple cutaneous nodules and the biopsy is the most important step to follow, but before that we need to talk about the possible etiologies of the nodules.

2.2. Cutaneous Sarcoidosis

Firstly, we judged whether or not our patient's nodules could be a manifestation of sarcoidosis, a pathology characterized by the

development of noncaseating granulomas in a variety of tissues including lung, mediastinal and abdominal lymph nodes, kidneys, heart and skin, suggestive biochemical (hypercalcemia) and bronchoalveolar lavage findings (lymphocytic alveolitis, elevated CD4/CD8 ratio). Cutaneous sarcoidosis has often been reported as an early finding and, along with erythema nodosum, nodules can be among the most frequent manifestations of this pathology [1]. However, the usual presentation was absent from our patient's clinical presentation. The chest radiography image was marked by the enlarged heart and interstitial lung edema, making it difficult to ascertain the presence of any possible mediastinal masses. Blood tests also showed no elevation in calcium levels, which would have supported such a diagnosis. Computer tomography examination did show lymph nodule enlargement in both the mediastinum and the abdomen, but their distribution and aspect were uncharacteristic of this pathology [2].

The patient being at the time hemodynamically precarious, we could not transfer her to a respiratory disease center for flexible fiberoptic bronchoscopy and bronchoalveolar lavage or transbronchial lung biopsy. In addition to that, her advanced cardiovascular impairment and symptomatology (NYHA Class IV) prohibited pulmonary functional testing, including spirometry, body plethysmography and diffusing capacity for carbon monoxide (DLCO).

Considering all these, biopsy and histopathological exam from the

cutaneous nodules remains the only viable investigation capable of confirming or excluding sarcoidosis.

2.3. Cutaneous Plasmacytoma

Secondly, we considered the possibility of cutaneous manifestations in the context of an underlying monoclonal gammopathy. Skin nodules can be the early signs of such a pathology, and represent either the infiltration and proliferation of malignant plasma cells, or the deposition of monoclonal immunoglobulin in nonmalignant monoclonal gammopathies [3]. In this context, we requested a hematological examination.

I examined a patient with complex cardio-vascular pathology, multiple, disseminated cutaneous nodules and a nodule in the right breast. In addition to this, the computer tomography examination showed enlarged lymph nodes in the mediastinum and abdomen. Blood tests show leukocytosis with neutrophilia, with no anemia or thrombocytopenia present. I also mention that blood protein electrophoresis showed no monoclonal peak. In this context I recommend capillary blood smear test, immunological screening for HIV (human immunodeficiency virus), HCV (hepatitis C virus), HBC (hepatitis B virus), HTLV (human T-lymphotropic virus 1) and biopsy with histopathological examination of tissue from breast and cutaneous nodules.

Following this we ran the immunological tests available to this hospital's laboratory, namely screening tests for HIV 1/2, HCV and HBC, all turning up negative. As a result, the only viable course of action remains biopsy with histopathological diagnosis.

2.4. Paraneoplastic Syndrome or Primary/Secondary Malignancy

The initial blood tests we ran at the admission of the patient presented some abnormalities that could be explained by the presence of malignancy, however more immediate causes had to be excluded before investigating such a diagnosis. These test results include hemolysis, inflammatory syndrome, including elevated fibrinogen and D-dimer levels, and altered INR and aPTT (which could have easily been explained by an overdose of Acenocumarol). A more specific finding is represented by the increased level of beta-2 microglobulin [4-8].

Following this consideration, we completed the blood tests with the malignancy markers available in this hospital (CA 19-9, CA 125 and CA 15-3), detecting increased blood levels. Keeping in mind the nodule discovered during initial evaluation in the right breast, we completed our imaging investigations with bilateral mammography and we requested an oncological examination.

The images show both breasts of mixed structure, predominantly fibro-glandular, with medium density, and relatively homogeneous aspect. In the right upper outer quadrant, extending towards the axilla, there is a speculated nodule, approximately 2.4/2.7 cm in diameter, extending towards the musculus pectoralis major, and with microcalcifications in its structure. Above the right nodule, in

the axillary region, there are two round nodules, 2.2/2.1, respectively 1/0.9 cm in diameter. There are also multiple enlarged lymph nodes (the larger being 0.6 cm in diameter) in the right axilla. In the left lower inner quadrant, we describe a nodule with irregular outline, around 1 cm in diameter. The final Breast Imaging Reporting and Database System (BI-RADS) score is B.5.

I detected a hard, mobile, non-painful nodule in the upper outer quadrant of the right breast, approximately 3 cm in diameter, extending towards the right axilla. In the lower inner quadrant of the left breast, a nodule with similar characteristics, but of lower volume (approximately 1 cm). Multiple nodules with diameters between 1 and 5 cm, diffusely disseminated on the posterior and anterior thorax, the larger of them being situated on the left posterior hemithorax. The patient has indication for biopsy and histopathological examination of tissue from right breast and left posterior hemithorax nodules, and contrast enhanced computer tomography of head, thorax and abdomen segments.

Following all these leads, we proceeded to the biopsy with the purpose of obtaining a final diagnosis.

2.5. Clinical Diagnosis

End-stage breast cancer with mediastinal and abdominal lymphatic dissemination, and cutaneous metastasis/paraneoplastic syndrome.

2.6. Diagnostic Testing

In order to confirm our suspicions, we effectuated biopsy from both the nodule in the right breast, and the largest cutaneous lesion, namely the nodule on the left posterior hemithorax. We managed to get enough tissue for both histopathological exams.

The first biopsy sample, from the right breast nodule, consists of seven tissue fragments, 0.2 cm in diameter and with lengths between 1.4 and 0.2 cm. These fragments contain breast tissue infiltrated with invasive ductal carcinoma of no special type (IDC), grade II, score 6 (tubule formation, 3 points; nuclear pleomorphism, 2 points, mitotic rate, 1 point). There is no lymphovascular or perineural invasion in the examined sample. The second biopsy sample, from the left posterior thorax nodule, consists of fibro-adipose tissue with carcinoma infiltrate, with an aspect compatible with IDC.

We also mention that cutaneous metastases are a relatively frequent manifestations in oncologic patients, with nodules being a known possible presentation of an underlying breast cancer [9].

2.7. Discussion of Management

During the hospital stay the patient developed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and consequently pneumonia. Of note is the fact that the patient was hospitalised during a local surge in coronavirus infection 2019 (COVID-19) cases. The infection responded initially to antiviral therapy and antibiotics, but her general state was not ameliorated.

Given the state of performance of the patient, with an Eastern Cooperative Oncology Group (ECOG) Performance Status Scale score of 4, and the fact that she also developed SARS-CoV-2 pneumonia during hospitalization, taking into account the stage of the disease and her medical history, following Oncology consult we decided to start her on an estrogen-receptor blocker (unfortunately, we did not have access to immunohistochemistry analysis at the time for technical reasons). She did not respond however to this treatment. There was no regression observed in her nodules and her general state. Her fragile hemodynamic parameters also did not improve. In this context, the case for chemotherapy was taken into consideration.

In spite of the antibiotic and supportive therapy her clinical condition was rapidly declining, the following days developing signs of multiple organ failure. Pain control medications were dispensed for her care, as the pain increased in intensity during her hospitalization, and morphine administrations eventually became necessary. In the course of several days her condition worsened and she died at 30 days after her admission to this hospital.

3. Conclusion

3.1. Final Diagnosis

Newly diagnosed end-stage invasive ductal carcinoma, complicated by SARS-CoV-2 pneumonia in elderly patient with advanced cardio-vascular pathology, resulting in exitus.

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