The Breast and the Lung in systemic granulomatoses

A challenging cohabitation

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ABSTRACT

Breast involvement in granulomatous disease is rare and may mimic cancer, while breast cancer may develop in the course of any systemic granulomatosis. We reviewed records of patients with breast disease and granulomatosis. Six females were included, all of whom diagnosed at some point with granulomatosis and a breast lesion either mimicking, breast involvement of the systemic disease, or proved to be breast cancer. This study reports the challenging cohabitation of breast cancer and any systemic granulomatosis. The rarity of said combination excludes possible pathogenetic relationship. What still remains a challenge is the unveiling of breast cancer in granulomatous diseases.
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1. INTRODUCTION

Both sarcoidosis and granulomatosis with polyangiitis (GP), otherwise known as Wegener's granulomatosis, are systemic granulomatous disorders of unknown etiology that may involve any organ or tissue[1-3]. Chronic eosinophilic pneumonia (CEP), although not a systemic granulomatous disease, may present with granulomas in histopathology in a consistent minority[4,5].

Breast involvement seldom occurs in the above two systemic granulomatoses and even more rarely, do breast nodules constitute the presenting manifestation in both sarcoidosis and GP[6-8]. In any case, given the fact that in female patients it is the most common malignancy, breast cancer should always be excluded, especially as it may occur in an already established sarcoidosis[9,10]. We aim to describe our experience with patients presenting with the challenging combination of the above diseases in both organs.

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2. METHODS AND PATIENTS

We retrospectively reviewed the medical records of all patients diagnosed with breast disease and lung or systemic granulomatosis in a tertiary university hospital from 2014 to 2018. Epidemiological, clinical, radiological, functional and histopathological data were extracted and analyzed after patient's informed consent. Diagnosis of breast cancer, sarcoidosis, Wegener's granulomatosis and eosinophilic pneumonia were according to international consensus criteria[1,2,9]. The study was approved by the Medical Ethics Committee of "Attikon" University Hospital, Greece (ΕΒΔ 258/29-5-14).

3. RESULTS

Six female patients were included in the study. Their age ranged from 40 to 56 years and half of them were non-smokers. Sarcoidosis was documented in 4 patients. In the first patient sarcoidosis and breast cancer were diagnosed concomitantly during the work-up for sarcoidosis. The second one developed breast cancer 5 years post sarcoidosis onset, and the third patient presented with sarcoidosis 5 years post breast cancer diagnosis. The fourth patient presented with a breast nodule containing epithelioid non-necrotizing granulomas in the ambit of a newly emerging sarcoidosis. The fifth patient's surgical excision of a breast nodule, detected in a background of systemic manifestations disclosed Wegener's Granulomatosis. Finally, our last patient developed eosinophilic pneumonia as a paraneoplastic syndrome of a lung metastatic breast cancer that was diagnosed and treated 5 years before.

3.1. Patients' description

The first patient was an asymptomatic 46-year-old non-smoker female evaluated for an accidentally discovered asymmetrical bilateral hilar enlargement (Figure 1a). A whole-body ^{18}F-fluoro-2-deoxyglucose positron emission computed tomography (^{18}F-FDG PET/CT) revealed significantly increased radiotracer uptake of the hilar and mediastinal lymph nodes as well as of the right supraclavicular lymph nodes (Figure 1b). A lesion of the lower-outer quadrant of the left breast (SUV_{max}=3.2) was also discovered. (Figure 1c) Multiple, discrete, focally confluent epithelioid non-necrotizing granulomas, compatible with sarcoidosis were documented through supraclavicular lymph-node surgical biopsy. The diagnosis of invasive ductal adenocarcinoma of the breast (Grade III) ER(-), PR(-) and HER2(+) was concomitantly evoked through surgical excision of the lesion.

The second report regards a 56-year-old non-smoker female patient who developed invasive lobular carcinoma of the breast (Grade II) ER(+), PR(+) and HER2(-) 5 years post sarcoidosis onset. Self-evaluation revealed a left breast mass that was further investigated by expert surgical clinical examination, mammography and surgical excision.

The third patient was a 55-year-old non-smoker asymptomatic female patient with a history of invasive ductal carcinoma (Grade II) ER(+), PR(+) and HER2(-) of a right accessory breast treated 5 years before. Two years after hormonal therapy, the disease relapsed necessitating

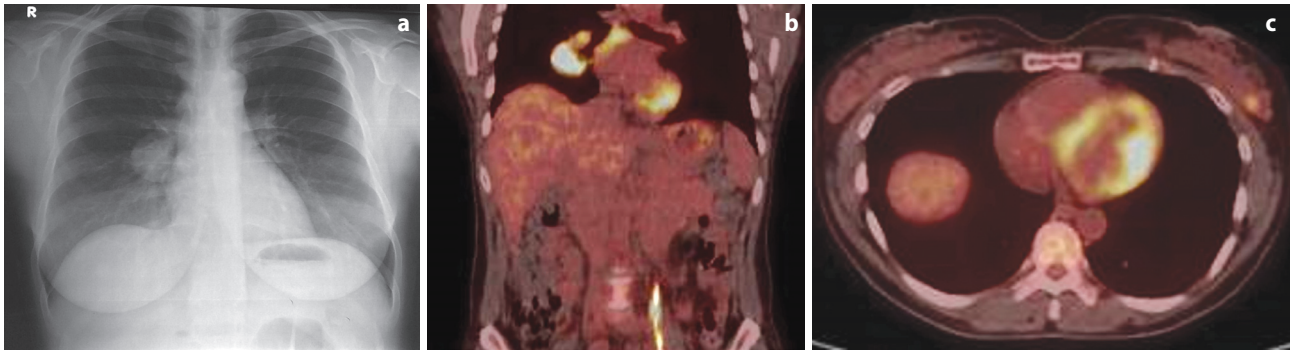

FIGURE 1. a, b. Posteroanterior chest radiograph of a 46-year-old non-smoker female patient disclosing asymmetrical bilateral hilar enlargement in a configuration characteristic of enlarged lymph nodes. ^{18}F-fluoro-2-deoxyglucose positron-emission-tomography computed-tomography (^{18}F-FDG-PET/CT) documented extensive mediastinal and hilar lymphadenopathy, especially on the right (SUV_{max}=7.8). The diagnosis of sarcoidosis was established by biopsy of supraclavicular lymph nodes. **c.** Increased radiotracer uptake was also detected at the inferior outer quadrant of the left breast (SUV_{max}=3.2) evoking further work-up for breast cancer that was documented through surgical excision of the lesion.

surgery, chemotherapy and radiotherapy followed once again by hormonal therapy. A routine yearly follow-up chest-CT 5 years post initial breast cancer revealed multiple micronodular (milliary type) lesions predominantly in the upper lung fields not existing in previous examinations (Figure 2). Increased serum Angiotensin Converting Enzyme (SACE) of 45.10 U/L (normal <42 U/L) and a lymphocytic bronchoalveolar lavage (35% lymphocytes) with a CD_4/CD_8 ratio of 7.6 led to the diagnosis of sarcoidosis. Apart from increased radiotracer uptake in the hilar and mediastinal lymph nodes (SUVmax=5.4) at ^{18}F-FDG PET/CT, no other sites of activity were revealed neither at the micronodular lesions nor at the breasts and axilla regions

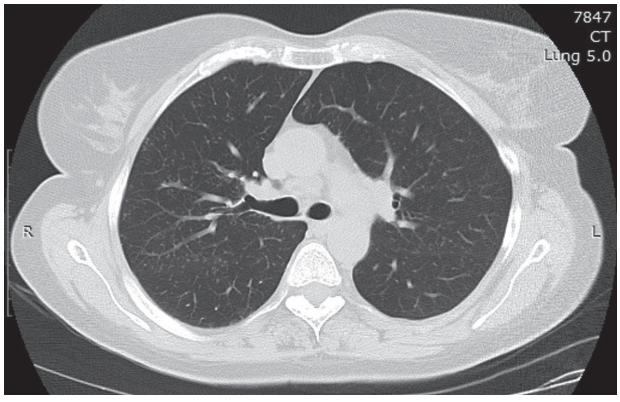

FIGURE 2. High resolution computerized tomography (HRCT) scan at the level of the carina demonstrating multiple micronodular lesions (milliary pattern). It regards a 55-year-old non-smoker female patient with a history of adenocarcinoma of the breast 5 years before. No findings of relapse of the disease were documented and the diagnosis of sarcoidosis was established based on a combination of clinical, laboratory, bronchoscopic and ^{18}F-FDG-PET/CT findings.

Our fourth patient, a 40-year-old smoker female, underwent surgical excision of a palpable lesion in her left breast thus permitting the diagnosis of newly appearing sarcoidosis by revealing the presence of incompletely formed non-necrotizing granulomas compatible with sarcoidosis in an intramammary lymph node.

The fifth patient presented with a palpable mass in the right breast (Figure 3a) and with systemic manifestations including dry cough, fatigue, anorexia, low grade fever and body weight loss. Surgical excision of the subareolar breast nodule disclosed poorly formed granulomas, surrounded by palisading histiocytes and giant cells with central necrosis extending to the walls of arteries and veins compatible with granulomatosis with polyangiitis. She was cANCA [proteinase 3 antineutrophil cytoplasmic antibodies (PR3-ANCA)] positive and the lungs (multiple nodular lesions) (Figure 3b, 3c) and the left eye (scleritis) were also involved.

Finally, our last patient, a 54-year-old ex-smoker female presented with fever, newly appearing dyspnea on exertion and a chest CT revealing multiple bilateral infiltrates (Figure 4). She had a history of surgically treated ductal invasive breast carcinoma (Grade III) ER(-), PR(-) and HER2(+) and had also received adjuvant chemotherapy and radiotherapy 5 years before. She received glucocorticosteroids for a presumptive diagnosis of eosinophilic pneumonia based on peripheral blood and bronchoalveolar lavage eosinophilia. During prednisolone tapering symptoms relapsed and the chest CT showed newly formed infiltrates

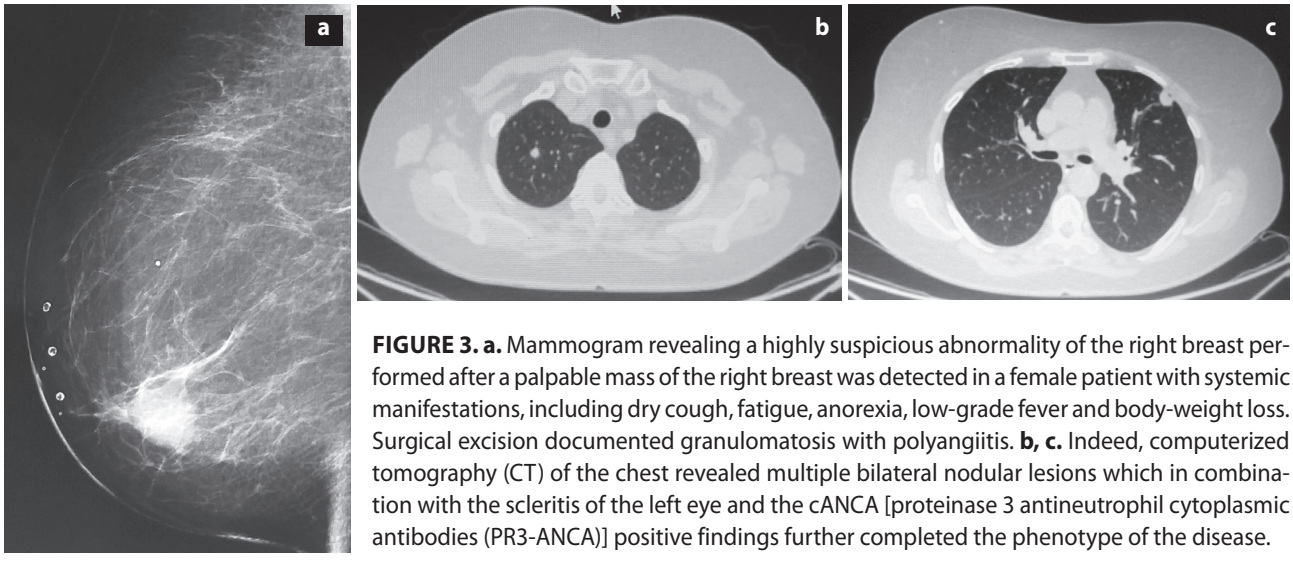

FIGURE 3. a. Mammogram revealing a highly suspicious abnormality of the right breast performed after a palpable mass of the right breast was detected in a female patient with systemic manifestations, including dry cough, fatigue, anorexia, low-grade fever and body-weight loss. Surgical excision documented granulomatosis with polyangiitis. **b, c.** Indeed, computerized tomography (CT) of the chest revealed multiple bilateral nodular lesions which in combination with the scleritis of the left eye and the cANCA [proteinase 3 antineutrophil cytoplasmic antibodies (PR3-ANCA)] positive findings further completed the phenotype of the disease.

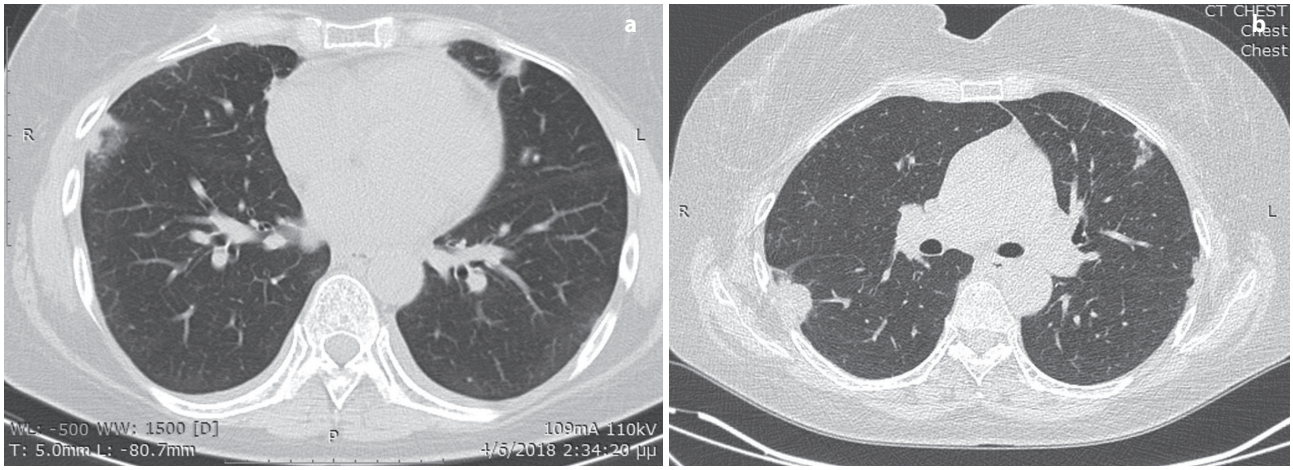

FIGURE 4. a. Computerized tomography of the chest revealing multiple bilateral peripheral infiltrates. It regards a 54-year old ex-smoker female patient with fever and newly appearing dyspnea. The patient had a history of surgically treated ductal invasive breast carcinoma (Grade III) and had also received adjuvant chemotherapy and radiotherapy 5 years before. She was initially treated with corticosteroids for a presumptive diagnosis of eosinophilic pneumonia based on peripheral blood and bronchoalveolar lavage eosinophilia. Newly formed infiltrates with cavitating nodules and masses developed and managed with antimicrobials and higher prednisone dosage. **b.** Clinical and radiological improvement was achieved thus revealing on a repeat chest CT a solitary right lung nodule. Surgical lung wedge excision of the lesion confirmed the diagnosis of metastatic breast cancer.

and cavitating nodules and masses. Clinical and radiological improvement was achieved with antimicrobials and higher prednisone dosage thus revealing a solitary right lung nodule. A surgical lung wedge excision was performed confirming metastatic breast cancer. In this case, eosinophilic pneumonia presumably developed as a paraneoplastic syndrome of a lung metastatic breast cancer diagnosed and treated 5 years before.

4. DISCUSSION

This study presents the challenging involvement of the breast in systemic granulomatoses which although rare may present a multitude of clinical scenarios: a) the breast as the first manifestation of systemic granulomatosis both in sarcoidosis and GP (2 patients), b) development of breast cancer in the course of an already established and diagnosed sarcoidosis (1 patient), c) breast cancer as an accidental finding during sarcoidosis work-up (1 patient) d) sarcoidosis onset in a patient with a history of breast cancer (1 patient) and finally, e) metastatic breast cancer triggering the development of chronic eosinophilic pneumonia as a paraneoplastic syndrome.

The development of sarcoidosis and breast cancer in the same patient is considered a rather unusual co-habitation[6,10]. According to previous studies, sarcoidosis usually precedes breast cancer in approximately half of the patients; sarcoidosis follows breast cancer in one third of the patients and in the remaining both diseases develop almost concomitantly. In our case series, all three chronological connections were represented. The above-mentioned great variation of chronological association does not support any clear pathogenetic association between sarcoidosis and breast cancer although larger studies are needed to shed light on such a serious aspect of this cohabitation. Irrespective of the above considerations, any newly discovered breast lesion necessitates extensive imaging work-up by mammography, breast ultrasound, breast MRI and/or PET/CT as well as pathologic examination for documentation of its behavior. This is in accordance with the already published data recommending histological study of mammary lesions presenting either as a new finding or as a secondary finding in the background of another granulomatous or systemic disease[6,9,10].

In our case series, this approach permitted us to document through breast pathology the first manifestation of either sarcoidosis or GP. Breast involvement in sarcoidosis and GP is scarce and constitutes a diagnostic challenge for both the surgeon and the pathologist, especially when they consist the presenting site of disease development. In that case the differential diagnosis includes more frequent causes of granulomatous mastitis such as breast cancer with sarcoid-like reactions, foreign body reactions, infec-

tions and rheumatoid nodules[11,12]. A detailed evaluation of other signs and symptoms characteristic of each disease as well as specific serologic data may contribute to the final diagnosis. In case of uncertainty a second biopsy of another involved organ (e.g. the lung) may be determinant.

Surgical excision may also unveil the association between the breast and the lung in various atypical presentations of this challenging cohabitation. In our last patient eosinophilic pneumonia characterized by migrating infiltrates with BAL and peripheral eosinophilia was presumably triggered as a paraneoplastic syndrome of a lung metastatic breast cancer. To our knowledge this is the first report of such a paraneoplastic syndrome concerning breast cancer. Surgical biopsy of a remaining lung infiltrate after corticosteroid treatment contributed to the documentation of its metastatic nature. The inclusion of CEP in lung granulomatoses although arbitrary has its source on the fact that occasionally granulomas share the field with eosinophils in CEP histopathology[4,5,13].

5. CONCLUSION

In conclusion, this study reports the unusual and challenging cohabitation of breast cancer and any systemic granulomatous disease. Especially in sarcoidosis this may occur at any point of its clinical course. The rarity of said combination excludes any possible pathogenetic relationship. What still remains a challenge is the unveiling of breast cancer in granulomatous diseases.

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Ethical approval: The study was approved by the Medical Ethics Committee of "Attikon" University Hospital, Greece (ΕΒΔ 258/29-5-14).

Declaration of conflict of interest: All authors declare that they have no conflict of interest related to this work.

ΠΕΡΙΛΗΨΗ

Ο μαστός και οι πνεύμονες στις συστηματικές κοκκιωματώδεις νόσους. Μια προκλητική «συγκατοίκηση»

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Η συμμετοχή του μαστού στις συστηματικές κοκκιωματώδεις νόσους είναι σπάνια και μπορεί να μιμηθεί καρκίνο του μαστού, ενώ από την άλλη πλευρά ο καρκίνος του μαστού μπορεί να αναπτυχθεί κατά τη φυσική πορεία κάθε συστηματικής κοκκιωματώδους νόσου. Ανασκοπήσαμε τα αρχεία ασθενών με νόσο του μαστού και κοκκιωματώδη νόσο. Η μελέτη συμπεριέλαβε έξι γυναίκες ασθενείς, όλες από τις οποίες έφεραν διάγνωση κάποιας μορφής κοκκιωματώδους νόσου και βλάβης του μαστού η οποία είτε αποδόθηκε στη συμμετοχή του οργάνου στη συστηματική νόσο είτε αποδείχτηκε ότι ήταν καρκίνος του μαστού. Η μελέτη αυτή κάνει αναφορά στην προκλητική συνύπαρξη καρκίνου του μαστού και συστηματικής κοκκιωματώδους νόσου. Η σπανιότητα του συνδυασμού αυτού αποκλείει το ενδεχόμενο πιθανής παθογενετικής σχέσης. Αυτό που αποτελεί εντούτοις σημαντική πρόκληση είναι η αποκάλυψη του καρκίνου του μαστού σε ασθενή με συστηματική κοκκιωματώδη νόσο.

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Λέξεις - Κλειδιά: *Μαστός και Πνεύμονες, Σαρκοείδωση, Πολυαγγειίτιδα, Κοκκιωματώδης νόσος, Ηωσινοφιλική Πνευμονία*

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