Dermatomyositis and breast cancer: a multicenter Tunisian retrospective study of 13 cases

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RÉSUMÉ

But : Evaluer les particularités épidémiologiques, cliniques, paracliniques et pronostiques chez les patientes atteintes de dermatomyosite (DM) et cancer du sein.

Méthodes: Les données cliniques, paracliniques et évolutives de 13 patientes atteintes de DM et cancer du sein ont été rétrospectivement colligées parmi 250 DM répertoriées entre Janvier 1982 to décembre 2009.

Résultats: La moyenne d'âge était de 47±18 ans. La DM avait précédé le cancer du sein dans 3 cas, était concomitante au cancer dans 2 cas et survenait après la néoplasie dans 8 cas. Cliniquement, des lésions ulcérées et bulleuses prédominant aux membres étaient notées dans 2 cas. Un déficit musculaire proximal sévère était observé dans 4 cas et une patiente avait présenté une dermatomyosite amyopathique. Le cancer du sein était classé stade IV de la classification TNM dans 3 cas, stade IIIA dans 2 cas, stade IIB dans 3 cas, stade IIA dans 3 cas et stade I dans 2 cas. Neuf patientes avaient noté une nette amélioration de la DM après traitement du cancer du sein. Cinq patientes sont décédées de récidives loco-régionales ou de métastases à distance (mortalité de 41.66%). La survie médiane était de 35 mois (3-177) après le diagnostic de DM.

Conclusion: En Tunisie, la DM semble associée à une incidence élevée de cancer du sein. Une évolution paranéoplasique de la DM est notée dans 70% des cas. En raison du risque élevé de cancer du sein dans notre pays, outre l'examen clinique minutieux et les examens biologiques de routine, une mammographie, une radiographie du thorax et un examen gynécologique sont recommandés chez toute femme âgée de plus de 40 ans, atteinte de DM, notamment en cas d'antécédents personnels ou familiaux de cancer du sein.

Mots-clés
Dermatomyosite, Cancer, sein, paranéoplasique

SUMMARY

Aim: To evaluate the epidemiological, clinical, biological features and prognostic factors in patients presenting an association of dermatomyositis (DM) and breast cancer (BC).

Methods: Medical records of 13 patients with DM and BC among 210 DM collected from January 1982 to march 2009 were retrospectively reviewed.

Results: Mean age was 47±18 years. DM preceded BC in 3 patients, was concurrent with BC in 2 cases and followed it in 8 cases. Clinically, ulcerative and bullous lesions predominating on limbs were observed in 2 patients. A severe proximal muscular weakness was observed in 4 cases and one patient has presented an amyopathic dermatomyositis. BC was staged IV in 3 pts, IIIA in 2 cases while 3 had stage IIB, 3 stage IIA and 2 stage I according to TNM classification. Nine out of 13 patients had parallel improvement of DM symptoms after treatment of BC. Five patients died of recurrence or distant metastasis (mortality 41.66%). Median survival was 35 months (3-177) after DM diagnostic.

Conclusion: In Tunisia, DM is associated with an increased incidence of BC. A paraneoplastic course of DM is noted in 70% of patients. In view of the increased risk of BC in our country, in addition to routine examination and laboratory screening, mammography, chest ultrasound, and gynaecological examination, are indicated in women with DM older than 40 years, particularly in case of previous personal or familial history of breast neoplasm.

Key-words
Dermatomyositis, Cancer, Breast, female malignancy, paraneoplastic

Dermatomyositis (DM) is an uncommon idiopathic inflammatory myopathy with characteristic cutaneous manifestations and its association to several neoplasms is well known, reported in around 15 to 30% of DM patients (1-3).
The most frequently reported cancers are gynaecological ones (breast and ovary) among women and lung cancer among men as well as nasopharyngueal and gastrointestinal malignancies in both sexes (2, 3).
According to the 1999¬2003 North Tunisia Cancer Registry, Breast cancer (BC) is the first female malignancy with a standardised incidence of 29.2/100000 habitants and a mean age of occurrence of 50.7 years with 10.9% of them younger than 35 years (4).
Our retrospective descriptive study aims to analyze clinical and laboratory characteristics of DM associated with breast cancer and to evaluate prognostic factors of this association

PATIENTS AND METHODS

We retrospectively collected all cases of DM associated with breast cancer (BC) in 8 University hospitals of Tunisia from January 1982 to March 2009.
DM diagnosis was based on Bohan and Peter's criteria (5). We collected the following data: sex, age at the time of diagnosis of DM, chronology of DM as related to cancer, stage of BC, biological findings, electromyographic analysis, muscular biopsy, treatment of cancer and DM, therapeutic response of cancer and DM and follow up from initial diagnosis of cancer and DM. Tumors were classified according to the TNM breast cancer stage (6).

RESULTS

Thirteen cases of DM associated with BC were recorded among 210 DM collected during this period (1982-2009) (table 1). Among gynaecological neoplasms, there were also 3 ovarian cancers. Mean age of DM/BC patients was 47± 18 years and 9 women were younger than 50 years at BC diagnosis. DM preceded BC of 4 months in 2 cases and 3 years in one case. It was concomitant to BC in 2 cases and occurred after BC in 8 cases with a mean delay of 28 months ± 23. Clinically, eyelid erythema was present in all patients and facial erythroedema was objected in 5 cases (figure 1). Gottron's papules were observed in 5 cases, periungual erythema was noted in 6 patients and poikilodermic erythema of the trunk was present in 3 cases (figure 2). Ulcerative and bullous lesions predominating on limbs were observed in 2 patients. A severe proximal muscular weakness was objected in 4 cases. Biological analyses showed an increased level of creatin phosphokinase (CPK) (10 to 20 times the normal value) in 3 of the 4 patients with a severe muscle weakness. One patient had an amyopathic dermatomyositis with a mild muscular weakness, normal muscular enzymes and normal electromyographic aspect. This DM sine myositis occurred 12 months after BC diagnosis. Concerning TNM staging, 3 had stage IV (M1) breast cancer, 2 had stage IIIA, 3 stage IIB, 3 stage IIA and 2 stage I. Treatment of DM consisted of prednisone (1-2 mg/kg/day) in all patients with progressive reduction of the doses within a median period of 4 months (1-10months).

Figure 1 : Facial erythroedema

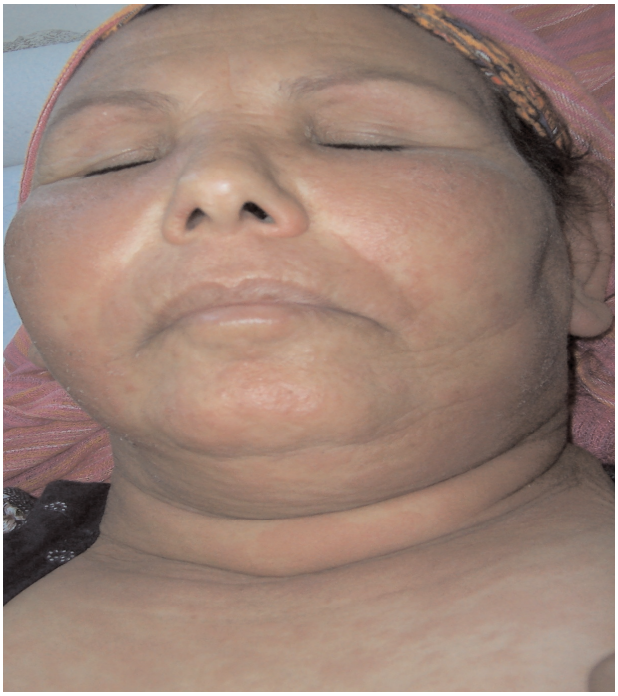

Figure 2 : Gottron's papules and periungueal erythema

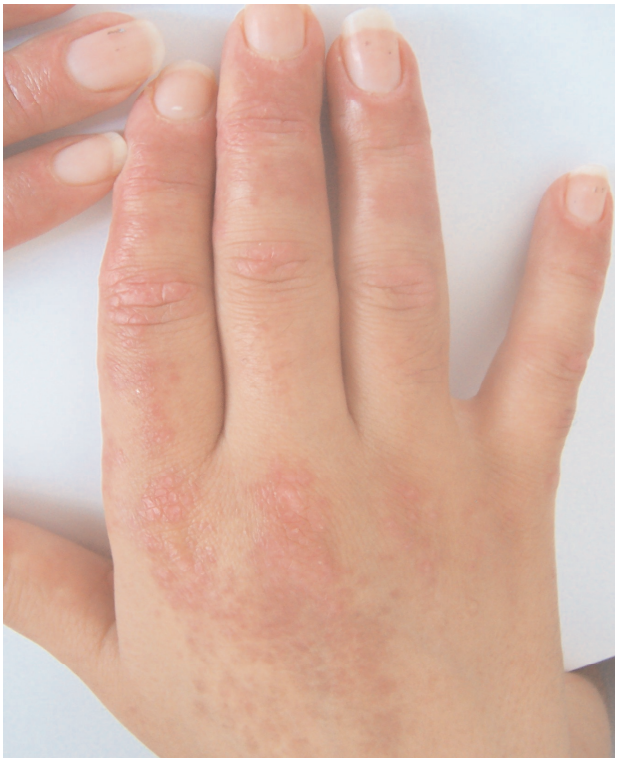

Table 1 : Characteristics of DM with breast cancer in our patients

Case N°	Age (years)	Chronology DM/C	Cutaneous signs	Muscular weakness	CPK/LDH	EMG	Treatment	Evolution
1	49	5 months after	EE,	+	CPK (2x) LDH (2x)	+	Corticosteroïds Radio T Chemo T	CR 87months/DM 92months/cancer
2	46	3 months before	EE, GP,	+	LDH (2x)	+	Corticosteroïds surgery Radio T Chemo T	CR 177months/DM 174months/cancer
3	29	48 months after	EE, GP,	+++	LDH (2x)	+	Corticosteroïds surgery Radio T Chemo T	Died 12months/DM 60months/cancer metastases
4	44	3 months before	EE, PE, PUE	+++	CPK (12x) LDH (2x)	+	Corticosteroïds Radio T Chemo T	CR 6months/DM 3months/cancer
5	46	Concomitant	EE, PE,	+	CPK (10x) LDH (2x)	+	Corticosteroïds surgery	CR: 6months after DM/cancer lost of view
6	62	120 months after	EE, PUE	+	CPK (5x) LDH (3x)	+	Corticosteroïds surgery Radio T	Died 3months/DM 123 months/cancer metastases
7	53	12 months after	EE	+++	CPK (9x) LDH (2x)	+	Corticosteroïds Chemo T	CR 6months/DM 18months/cancer
8	46	concomitant	EE, GP	+	CPK (2x) LDH (2x)	+	Corticosteroïds Chemo T	Died 36months/DM and cancer
9	43	12 months after	EE, PE	+	CPK (2x) LDH (2x)	+	Corticosteroïds surgery Radio T Chemo T	Died 12 months/DM and 24 months /cancer metastases
10	42	9 months after	EE, PUE	+	CPK: (2x) LDH :(3x)	+	Corticosteroïds Radio T Chemo T	metastases
11	57	5 months after	EE, GP Ulcerative and bullous lesions on limbs	+++	CPK: (20x)	+	Corticosteroïds Chemo T	Died 4 months/DM 9 months/ cancer
12	49	12 months after	EE, GP,PUE Ulcerative and bullous lesions on limbs	-	normal	normal	Corticosteroïds surgery Radio T Chemo T	CR 12 months/DM 24 months/K
13	50	36 months before	EE, PUE	++	CPK (9x) LDH (7x)	+	Corticosteroïds surgery	CR 38 months/DM 2 months/K

Legend: EE: eyelid erythema, GP: Gottron papules, PE: poikilodermic erythema, PUE: periungial erythema, DM: Dermatomyositis, K : cancer, Chimio T : Chemotherapy, Radio T : Radiotherapy CR : clinical remission.

Treatment of BC consisted of exclusive surgery in 2 cases, palliative radiotherapy in 1 case, radio-chemotherapy in 3 cases, chemotherapy in 3 cases, and a combination of 3 treatments in 3 cases. Adjuvant chemotherapy regimen used in our patients was FEC 100 (Epiadriamycin: 100mg/m2, 5 fluorouracil 500mg/m2 and cyclophosphamid 500mg/m2), administered every 3 weeks during 6 cycles. With a median follow-up of 21 months (3 to 60), nine out of the 13 patients had parallel improvement of DM after treatment of BC. In 4 cases, flare up of DM has revealed visceral metastases of BC (pulmonary, hepatic or bone's metastases). Five patients died of recurrence or distant metastasis (mortality of 41.6%). Median survival was 35 months (3 to 177) after DM diagnostic.

DISCUSSION

The most commonly reported female malignancies associated with DM are mainly those of the breast and the ovary (2, 3, 7, 8). In a literature review of Callen (2) in 1982, 367 cancers associated to DM have been reported, with 33% of them gynaecological (breast cancer representing 17.4% of all cases with 64 cases.

In our world literature review in 2000, gynaecological cancers were also the most frequent neoplasms associated with DM (207/695) dominated by the ovarian (13%) and breast (11.5%) cancers (3). In a pooled analysis of published national data from Sweden, Denmark, and Finland, Hill (8) identified 618 cases of DM, among whom 198 associated with cancer.

Dermatomyositis was strongly associated with malignant disease [Standardised incidence ratio: (SIR) 3·0, 95% CI 2·5–3·6], particularly ovarian (10·5, 6·1–18·1), lung (5·9, 3·7–9·2), pancreatic (3·8, 1·6–9·0), stomach (3·5, 1·7–7·3), colorectal (2·5, 1·4–4·4) cancers, non-Hodgkin lymphoma (3·6, 1·2–11·1) and breast cancer (2·2, 1·2–3·9).

Breast neoplasm (BC) is the first malignancy in Tunisian women. It represents the first cause of mortality in Tunisian female patients (4). In a previous Tunisian study, DM was associated with cancer in 15.3% of cases (3). BC has represented with nasopharyngeal carcinoma the 2 most common neoplasms associated with DM (3).

The mean age of patients with DM at diagnosis of BC is habitually more than 50 years (4-8). In a retrospective study of 8 cases of BC and DM, Yeh (9) has noted that the mean age of patients was 62.1 +/- 6.7 years.

The 47 years young mean age noted in our study could be partially explained by the demographic pyramid patterns in Tunisia compared to western countries (4). Four of our patients were younger than 45 years old at BC diagnosis.

Pathogenesis of paraneoplastic syndromes is still poorly understood. These disorders may be caused by tumour production or depletion of biologically active hormones or growth factors.

In several paraneoplastic dermatoses, antigen cross-reactivity between tumour and skin, called "molecular mimicry" may lead to aberrant recognition of normal tissues after viral mediated transformation and cause skin changes (10, 11).

Clinically, two patients have developed ulcerative and bullous lesions of limbs suggesting a particular association with cancer (12, 13). A severe proximal muscular weakness which is not predictive of the presence of cancer was present in 4 cases. Amyopathic dermatomyositis has been associated with both recurrent and newly diagnosed breast carcinoma (14). Metastatic BC can itself mimic cutaneous signs of DM especially in its inflammatory and neglected forms (15).

In our series, only one patient has developed an amyopathic DM, 12 months after BC diagnosis.

Some biological studies have looked for the seric muscular enzyme profile in paraneoplastic DM.

Selvaag (16) has noted an elevation of seric muscle enzymes in 78% of cases of DM and cancer versus 34% of those with DM sine cancer. In our study, 3 of the 4 patients having a severe muscular weakness have increased levels of creatine kinase (> 10 times the normal value).

Dermatomyositis habitually occurs at the same time as the internal malignancies do, and follows a parallel course (remission of DM after removal of cancer and relapse when reappearance of malignancy) (2, 3, 7, 8). In our series, 9 out of 13 DM (70%) had a paraneoplastic course.

In some cases, however, because cancer may be asymptomatic for years, DM may be recognized long before cancer is diagnosed, justifying a protocol of screening work up in endemic areas of some neoplasms (8,17). According to Hill (8), among cancers diagnosed before DM, most (71%) preceded myositis by 2 years or less. Besides, for all cancer types, there was a three-fold increase in risk of malignant disease after diagnosis of DM.

Thus, when DM heralds a new or recurrent cancer, recognition of these conditions can lead to earlier detection and treatment of the underlying malignancy (18).

In a recent US study about BC risk in elderly women with systemic autoimmune rheumatic diseases, those diagnosed with rheumatoid arthritis were less likely to develop breast cancer (OR=0.87, 95% confidence interval (CI)=0.82–0.93).

The risk reduction did not differ by tumor ER-status (OR=0.83 for ER-positive vs OR=0.91 for ER-negative). They concluded that systemic inflammation may affect breast epithelial neoplasia (19).

Prognosis of DM associated with BC is more severe than the idiopathic form, probably related to the type advanced stages of cancers and their delayed diagnosis (17, 20). In our series, most of the neoplasms (8/13) were diagnosed at advanced stage.

Mortality rate, in case of DM associated with cancer, is relatively high ranging from 25 to 75% (19-21). The main cause of death is recurrence or distant metastasis.

According to Xue (21), actuarial survival at 2 and 5 years were respectively 75% and 50% and death was mainly due to cancer. In our study, 5 patients died of recurrence or distant metastasis (mortality 41.66%). Median survival was 35 months (3-177) after DM diagnostic.

CONCLUSION

Most cases of paraneoplastic DM parallel the clinical course of breast neoplasm. Sudden occurrence of DM later in life, rapid course, unusual and more severe clinical presentation, could suggest a paraneoplastic course of DM.

These findings should prompt a thorough search for possible association with malignancies mainly those of breast and cavum in our country, as well as a way to monitor tumour recurrence in case of known cancer.

Références

1. Stertz G. Polymyositis. Berl Klin wochenschr 1916; 53:489.
2. Callen JP. Dermatomyositis and malignancy. Clin Rheum Dis 1982; 8: 369-81.
3. Mebazaa A, Boussen H, Nouira R, et al. Dermatomyositis and malignancy in Tunisia: a multicenter national retrospective study of 20 cases. J Am Acad Dermatol 2003; 48:530-4.
4. Cancer Registry of the North of Tunisia, 1999-2003 data. Ministry of health of Tunisia. 2009.
5. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975; 20:403-7.
6. Wittekind C, Greene FL, Hutter RVP, Klimpfinger M, Sobin LH Eds. TNM atlas, 5th edition. Springer. 2006:180-94.
7. Callen.JP. Dermatomyositis and female malignancy. J Surg Oncol 1986; 32: 121-4.
8. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 2001; 357: 96-100.
9. Yeh CN, Chen SC, Hwang TL, Chen MF, Liaw CC, Chan HL. Breast carcinoma in patients with dermatomyositis: a retrospective analysis of eight cases. Chang Gung Med J. 2002; 25: 374-80.
10. Brenner S, Tamir E, Maharshak N, Shapira J. Cutaneous manifestations of internal malignancies. Clin Dermatol 2001; 19:290-7.
11. Chung VQ, Moschella SL, Zembowicz A, Liu V. Clinical and pathologic findings of paraneoplastic dermatoses. J Am Acad Dermatol. 2006; 54:745-62.
12. Kubo M, Sato S, Kitahara H. Vesicle formation in dermatomyositis associated with gynecologic malignancies. J Am Acad Dermatol 1996; 34:391-4.
13. Scheinfeld NS. Ulcerative paraneoplastic dermatomyositis secondary to metastatic breast cancer. Skin Med. 2006; 5:94-6.
14. Goyal S, Nousari HC. Paraneoplatic amyopathic dermatomyositis associated with breast cancer recurrence. J Am Acad Dermatol 1999; 41:874-5
15. Seishima M, Shimizu H, Oyama Z. Skin metastasis of breast cancer clinically undistinguished from amyopathic dermatomyositis. Eur J Dermatol. 2001; 11:131-3.
16. Selvaag E, Thune P. Dermatomyositis and cancer. A retrospective study. Tidsskr Nor Laegeforen 1994; 114:2378-80.
17. Airio A, Pukkala E, Isomaki H. Elevated cancer incidence in patients with dermatomyositis: A population based study. J Rheumatol 1995; 22:1300-3.
18. Cohen PR, Kurzrock R. Mucocutaneous paraneoplastic syndromes. Semin Oncol 1997; 24: 334-59.
19. Gadalla SM, Amr S, Langenberg P, et al. Breast cancer risk in elderly women with systemic autoimmune rheumatic diseases: a population-based case–control study. Br.J. Cancer 2009; 100: 817-21.
20. Chow WH, Gridley G. Cancer risk following polymyositis and dermatomyositis: a nationwide cohort study in Denmark. Cancer Causes Control 1995; 6:9-13.
21. Xue L, Chen X, Chen S. Prognostic factors of dermatomyositis: analysis of 119 cases. Chung Hua Nei Ko Tsa Chih 1997; 36:32-5.