Malignancy in a retrospective cohort of 17 patients with Dermatomyositis or Polymyositis in southern Tunisia

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Introduction. The prognosis of dermatomyositis (DM)/ polymyositis (PM) in adults is partly related to their association with neoplasia. The aim of our study was to report the epidemiologic, clinical, paraclinical, therapeutic and evolutionary aspects of DM associated with malignancy in patients from Sfax, south eastern of Tunisia.

Methods. A retrospective cohort study of patients with DM or PM admitted in Dermatology and Internal Medicine Departments of Hedi Chaker University Hospital of Sfax between 1996 and 2015. Cases of DM or PM associated with malignancy were retained.

Results. Seventeen cases (13.5%) of DM or PM associated with malignancy were noted. Fourteen patients had DM and 3 patients had PM. The Sex ratio M / F was 0.3 and the mean age at diagnosis was 56.5 years. In DM patients, malignancy preceded the myositis in 64.2% of cases. In PM patients, only one patient was known to have breast cancer and the myositis revealed the cancer for 2 others. Treatment consisted of corticosteroids associated with methotrexate in 4 cases. Outcome was fatal in 5 cases (29.4%), due to the underlying cancer in 3 cases. Swallowing disorders related to DM/PM were responsible for death in 2 cases.

Conclusion. There are no specific clinical or biological features in paraneoplastic DM. In our series, breast neoplasm represented the first cancer associated with DM. Cancers of nasopharynx, colon and urinary tract had the second position.

Keywords: dermatomyositis, polymyositis, cancer, paraneoplastic syndrome, risk.

INTRODUCTION

Dermatomyositis (DM) and polymyositis (PM) are autoimmune disorders characterized by inflammatory myopathy belonging to the group of connective tissue disorders. They are often idiopathic but may sometimes be associated with neoplasia. The association between DM and cancer has been reported since 1916 by Stertz [1]. Several studies since then had reported a 3- to 6-fold increase in the risk of malignancy in patients with DM [2]. The association between cancer and myositis is widely variable in literature series. The present study aimed to evaluate the prevalence of malignancy in patients with DM/PM in Sfax (South-Eastern of Tunisia). We also studied the characteristics of the major type of the associated cancer, patient's age and gender and its prognosis. We emphasize on risk factors that must alert clinicians to search for underlying cancer, referring to our literature findings.

MATERIAL AND METHODS

We conducted a descriptive and retrospective study of all cases of paraneoplastic DM/PM followed at the Dermatology and Internal Medicine Departments of Hedi Chaker University Hospital (a tertiary care center) between 1996 and 2015. Diagnosis was based on Bohan and Peter criteria. We collected epidemiological, clinical, paraclinical, therapeutic and outcome data from registered medical observations.

RESULTS

During 20 years, 126 cases of DM/PM were diagnosed. Seventeen were paraneoplastic (13.5%) distributed into 14 cases of DM and 3 cases of PM. For the whole group, at presentation, the mean age of patients was 56.5 years (range 34-83yr) and the sex ratio M/F was 0.3. Symptoms evolved for a mean period of 3.6 months (range: 1-23 months).

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In DM patients, mean age was 57.2 years (range: 34-83 years) and the sex-ratio M/F was 0.28. The main clinical manifestations were: impaired general condition (4 cases, 28.5%), erythrœdema of the face particularly the orbital rim (11 cases, 78%), periungual erythema (5 cases, 36%), Gottron's papules (1 case, 7%), and myalgia with proximal muscle weakness (12 cases: 85.7%). Skin necrosis was noted in only one patient and pruritus was present in 2 cases. Biological tests noted acceleration of erythrocyte sedimentation rate (ESR) (13 cases, 93%) and elevated muscle enzymes (11 cases, 78%). Elevated creatine phosphokinase (CPK) was constant except in 3 cases. Electromyography (EMG) findings were consistent with myositis in 64.2% of cases. Muscle biopsy performed in 5 patients confirmed the diagnosis in 4 cases. Two patients had amyopathic DM (11.7%). The majority of patients (9 cases; 64.2%) had been already diagnosed with neoplasia and the median time elapsed between discovery of cancer and diagnosis of DM was 2.8 years (range, 6 months - 12 years). Etiological investigations disclosed a latent malignancy in 35.7% of cases, mostly following the first year (8 cases, 57.2%) or at the same time of diagnosis of DM (3 cases, 21.5%). Associated cancers were: breast cancer (6 cases, 42.8%), nasopharynx carcinoma (2 cases, 14.2%), colon carcinoma (2 cases, 14.2%), urinary tract carcinoma(2 cases, 14.2%), ovary carcinoma (1 case, 7%) and malignant thymomas (1 case, 7%). After transient recovery of 10.6 months (range 2-24 months), DM recurred in 3 patients, announcing metastases (Table1).

In PM patients, only one patient had breast cancer diagnosed two years before PM. The diagnosis of malignancy followed the one of PM in two cases after a median time of 2 months (range, 1-3 months). Impairment of general condition and myalgia, with accelerated ESR and myolysis were constant. The diagnosis of PM was confirmed by EMG and muscle biopsy in the 3 patients. Associated cancers were breast carcinoma, gallbladder carcinoma and lymphoma (Table 2).

All patients were treated with corticosteroids at high doses and with methotrexate in 4 cases. A relapse was observed after initial improvement, in 3 cases of DM, and disclosed metastasis. Outcome was fatal in 5 cases (29.4%), due to the underlying cancer in 3 cases. Swallowing disorders related to DM/PM were responsible for death in 2 cases (Tables 1, 2).

DISCUSSION

DM and PM are rare inflammatory myopathies [3]. Their prognosis in adults is mainly determined by their association with neoplasia [4, 5]. The association of DM with cancer is well established since 1916 [1, 3], whereas the relationship between PM and cancer is weaker [6] but it is becoming more common [5, 7]. Paraneoplastic DM's frequency is variously estimated through different series [4, 8]. The incidence varies from 15 to 54% [4, 7-10]. In Tunisia, according to a multicenter retrospective study, it is estimated at 15% [10]. The incidence of cancer in DM is 5 to 7 times greater than that of the general population [7]. As in our study, the reported mean age of association myositis and cancer is 59.5 years [3] with a female predominance [10]. The risk of this association is higher among men over 50 years [7, 8, 11]. In children, this association has not been described yet. Paraneoplastic DM/PM has no specific clinical or paraclinical features [5]. In DM, cutaneous signs are always present and muscle symptoms appear simultaneously or later after skin involvement [5]. The neck and the back of the hands are electively involved [5]. Erythema is classic, appearing on outset or during the evolution of atrophy beaches. Zarrabi *et al*. reported a rare case of edematous paraneoplastic DM with florid subcutaneous edema [12]. In prolonged cases, poïkilo-DM can appear. DM associated with cancer is amyopathic in 22% of cases [4, 13, 14], this association was noted in 11.7% of cases in our study. Some cases reported mucinosis as the only manifestation of DM [15, 16]. Skin necrosis, observed only in one patient of our series, was reported in 62% of DM associated with cancer and in 7% of non-paraneoplastic DM [9]. High levels of muscle enzymes are common [9]. Elevated ESR, noted in 93% of our cases, was also noted in DM associated with cancer [5].

Poor prognostic factors in DM that must alert for the possibility of associated neoplasia are: older age (more than 50 years at diagnosis [3, 8, 17, 18]), rapid onset, extensive skin lesions [19], pruritus [4], necrosis [6] and increased ESR [20]. Several studies have also found that the presence of certain antibodies in myositis such as anti JO1, anti Mi2 and anti U1RNP is associated with a low risk of cancers [21]. Nevertheless, the anti-155/140 antibodies are associated with a higher risk of cancer in DM [22]. It was recently established that anti-SAE1, and previously reported anti-TIF1-γ and anti-NXP2

antibodies, are all associated with an increased risk of cancer in patients with DM/PM. It could be a tool for etiologic research of paraneoplastic DM/PM [23]. Unfortunately, these laboratory tests were not performed in our study because of the lack of suitable kit.

Table 1
Baseline patients characteristics in DM patients

Patients	Sex	Age (years)	Interval between the diagnosis of PM and the associated cancer	Cutaneous involvement	Other systemic involvements	Biological findings	Type of malignancy	Treatment	Outcome
Patient 1	F	49	96 mo after	Periorbital erythroedema Erythema of the trunk and upper limbs Periungual erythema	Myalgia with proximal muscle weakness	ESR 40 CPK 279 LDH 280 ANA(+)	Breast carcinoma	High-dose corticosteroids	Favorable
Patient 2	F	68	24 mo before	Periorbital erythroedema Erythema of sun-exposed areas; Face telangiectasia	Myalgia with proximal muscle weakness	ESR 80 CPK 500 LDH 809 ANA (+)	Nasopharynx carcinoma	High-dose corticosteroids + Methotrexate	Favorable
Patient 3	M	51	Concomitant	Periorbital oedema Erythema of legs and proximal interphalangeal joints	Effort-related fatigability Arthralgia, myalgia, proximal muscle weakness	ESR 53 CPK 114 LDH 350 ANA (+)	Urinary tract carcinoma	High-dose corticosteroids + Methotrexate	Relapse after transient improvement (metastasis)
Patient 4	M	68	12 mo before	Erythema of the face and the low-neckline Periungual erythema	Effort-related fatigability Dyspnea, cough Swallowing disorders	ESR 63 CPK 5241 LDH 591 ANA(+)	Colon carcinoma	High-dose corticosteroids + Methotrexate	Relapse after transient improvement (metastasis), then death (due to cancer)
Patient 5	F	60	12 moafter	Erythema of the low-neckline and the upper limbs	Effort-related fatigability Proximal muscle weakness	ESR 11 CPK 34 LDH 202 ANA (+)	Breast carcinoma	High-dose corticosteroids	Favorable
Patient 6	M	59	24 mo after	Erythema of the face, the upper limbs and the trunk	Proximal muscle weakness	ESR 14 CPK 64 LDH NR ANA NR	Nasopharynx carcinoma	High-dose corticosteroids	Favorable
Patient 7	F	51	120 mo after	Periorbital erythema Erythema of upper and lower limbs	Impaired general condition Polyarthralgia	ESR 17 CPK 1105 LDH 2134 ANA (-)	Breast carcinoma	High-dose corticosteroids	Favorable
Patient 8	F	83	Concomitant	Erythroedema of the face and the low-neckline	Myalgia	ESR 38 CPK 7504 LDH **NF** ANA (+)	Ovary carcinoma	High-dose corticosteroids	Death (due to cancer)
Patient 9	M	50	Concomitant	Erythroedema of the face and the upper limbs	Proximal muscle weakness Swallowing disorders	ESR 60 CPK 1848 LDH 600 ANA (-)	Neuroendocrine carcinoma of the colon	High-dose corticosteroids	Favorable
Patient 10	F	44	12 mo after	Eczema-like eruption of the face and the trunk Periungual erythema Gottron's papules	Proximal muscle weakness	ESR 86 CPK 502 LDH 330 ANA (+)	Breast carcinoma	High-dose corticosteroids	Favorable
Patient 11	F	59	24 mo after	Erythema of sun-exposed areas	Myalgia with proximal muscle weakness	ESR 32 CPK 225 LDH 548 ANA (-)	Breast carcinoma	High-dose corticosteroids	Favorable
Patient 12	F	34	6 mo after	Erythema of the hands, low-neckline and loins	Proximal muscle weakness	ESR 33 CPK NR LDH NR ANA NR	Thymoma	High-dose corticosteroids	Favorable
Patient 13	F	53	12 mo after	Periorbital erythema Erythema of limbs extension face	Asthenia Myalgia Proximal muscle weakness	ESR 19 CPK NR LDH NR ANA NR	Breast carcinoma	High-dose corticosteroids	Death (due to DM)
Patient 14	F	72	24 mo before	Erythema of sun-exposed areas and limbs extension face	Impaired general condition	ESR NR CPK NR LDH NR ANA NR	Urinary tract carcinoma	High-dose corticosteroids	Relapse after rtransient improvement (metastasis)

Abbreviations: F: female; M: male; ESR: Erythrocyte sedimentation rate; CPK: Creatine phosphokinase; LDH: Lactate dehydrogenase; ANA: Antinuclear antibodies; NR datum not recorded. Mo: months

Table 2
Baseline patients characteristics in PM patients

Patients	Sex	Age (years)	Interval between the diagnosis of PM and the associated cancer	Biological findings	Other systemic involvement	Malignancy	Treatment	Outcome
Patient 1	F	39	24 mo after	ESR 110 CPK 1303 LDH 1850 ANA NR	Asthenia	Breast carcinoma	High-dose corticosteroids	Death (due to cancer)
Patient 2	F	61	Concomitant	ESR 115 CPK 1407 LDH 979 ANA (-)	Asthenia Weight loss Myocarditis	Gallbladder carcinoma	High-dose corticosteroids + Methotrexate	Death (due to PM)
Patient 3	F	60	12 mo before	ESR 30 CPK 45 LDH 1160 ANA (+)	Arthralgia	Lymphoma	High-dose corticosteroids	Relapse after transient improvement (metastasis)

Abbreviations: F: Female; M: Male; ESR: Erythrocyte sedimentation rate; CPK: Creatine phosphokinase; LDH: Lactate dehydrogenase; ANA: Antinuclear antibodies; NR: datum not recorded. Mo: months

Table 3
DM/PM and type of associated malignancy in different populations

Study	Population	Study period	Number of patients	Sex/Age	(n) Malignancy	Types of malignancies
Stockton *et al.* [18]	Scotland	1982-1996	705	F (433) /M(272)	50	Oesophagus (1); stomach (3); colon (7); lung (19); breast (3); cervix uteri (2); ovary (2); prostate (1); bladder (1); unspecified (6); Hodgkin's disease (1); Non-Hodgkin's lymphoma (2)
Chen *et al.* [25]	Taiwan	1997-2007	1655	F (1141)/M(514)	95	Nasopharynx (30); lung (22); breast (9); uterine cervix (3); ovary (2); lymphoma/ leukemia (4); oropharynx and larynx (1); esophagus (1); liver/gallbladder; colorectum (5); stomach (1); pancreas (1); kidney (3); urinary bladder (2); melanoma (1); bone/joint (1); thyroid (2); metastatic cancers (2)
Limaye *et al.* [27]	South Australia	1980-2009	373	F(245)/M(179)	43	lung cancers (7), prostate cancers (6), colon cancers (4), lymphomas (4), Hodgkin's disease (2), leukaemias (3), breast (3), melanomas(2), skin cancers (3), bladder (3) endometrial (1) testis(1), unspecified, site (1), 1nasopharyngeal(1), pancreatic (1) and myelodysplastic syndrome (1)
Requena *et al.* [37]	Spain	1994-2013	12	F(6)/M(6)	12	Ovarian Cancer (3), Bladder cancer (3), Lung cancer (1), stomach (1), breast cancer (1), Prostate (1) and cervix (1), Non-Hodgkin lymphoma (1)
Our study	South Tunisia	1996-2015	126	F(93)/H(33)	17	Breast carcinoma (7), Gallbladder carcinoma (1), Lymphoma (1), Thymoma (1), Urinary tract carcinoma (2), Colon carcinoma (2), Nasopharynx carcinoma (2), Ovary carcinoma (1)

DM/PM could follow an already diagnosed cancer, as 10 of our patients, but it often precedes cancer by several months [17, 18]. The risk of cancer occurrence seems to be greater in the first year of DM/PM diagnosis [3, 6, 11, 24]. Associated cancers do not seem to differ from those frequent in general population [10]. In general, carcinomas are more frequent than sarcomas and lymphoproliferative tumors. These cancers are dominated by breast cancer in women (41% in our series) [7, 9, 25] and lung cancers in men [7, 9]. According to Hendren *et al*., the presence of DM is associated with more-advanced breast cancer stage and is most commonly associated with invasive ductal carcinoma [26]. Other cancers were reported especially colorectal cancers, cancers of the ovary [3], the nasophagynx, the prostate [27, 28]. But, all localizations are possible: kidney, thyroid, malignant thymoma or lymphoma. Cancers of unknown primary-related DM had also been reported [29]. Zhang *et al*. reported a rare case of occult breast cancer in a man associated to DM [30]. To date and to our knowledge related to

skin cancers, yet so common, had not been reported (Table 3: DM/PM and type of associated malignancy in different populations).

There is often a clear correlation between changes in DM and those of the associated cancer [27]. For some patients, cancer treatment results in DM improvement or even recovery from DM [33]. If metastases appear, DM may recur. The latter situation was noted in 3 of our patients. DM was reported in association to a recurrence of breast cancer [25].

Disclosure of a cancer in a patient with DM is a poor prognostic factor. Mortality ranges from 35 to 58% after 20 months and 7 years, respectively [10]. It reaches 100% in case of severe forms of DM [4]. DM may be fatal, by swallowing disorders associated with muscle impairment as in 2 of our patients, but death is linked to cancer in 90% of cases [10].

Etiopathogenesis of this paraneoplastic syndrome remains controversial [6, 7]. Some authors propose an alteration of the extracellular matrix of the skin by increased inflammatory and immunological reaction in patient's skin. DM and some cancers share etiologic factors [6].

As the pathophysiology of paraneoplastic DM/PM remains unclear, no standard treatment regimen has been established yet [34]. High-dose corticosteroids are suggested as the first-line therapy. It was the therapeutic choice for all our patients. Immunosuppressant drugs or IV human immunoglobulins are suggested as second-line therapy. Drugs administered in case of DM do not seem to increase the risk of cancers [6]. Searching for neoplasia in DM is discussed [3], this assessment is systematic in adults for some authors [9], mainly if they had a history of neoplasia, rapid onset of DM, recurrence or sudden worsening of previously stable DM [24]. Some authors recommended repeated investigations at regular intervals of 6 to 12 months after diagnosis to prevent discovery of cancer at advanced stage [35]. Gkegkes *et al*. had even suggested to perform systematic colonoscopy in these patients [36].

CONCLUSION

In adult patients with DM/ PM, the presence of predictive factors such as advanced age, impairment of general condition and accelerated ESR must alert clinicians to the possibility of associated neoplasia. Thorough physical examination and accurate investigations are needed to detect cancer at an early stage. In our series, breast neoplasm represents the first cancer associated with DM. Cancers of nasopharynx, colon and urinary tract have the second position. Our study confirms correlation between neoplasia and DM's outcomes. The limitations of our study are the small number of patients with cancer and it would have been interesting to make comparisons with DM/PM patients that had no neoplasias and search for some distinct characteristics.

Conflict of interest.The authors declare that there are not conflicts of interest.

Introducere. *Prognosticul dermatomiozitei (DM)/polimiozitei (PM) la adult este legată şi de asocierea cu neoplaziile. Scopul studiului a fost de a raporta caracteristicile clinice, epidemiologice, paraclinice, terapeutice şi de evoluţie ale pacienţilor din Sfax, sud-estul Tunisiei, care aveau DM şi asociau şi malignităţi.*

Materiale. *A fost realizat un studiu retrospectiv (1996-2015) pe pacienţii cu DM sau PM internaţi în clinicile de Dermatologie şi Medicină Internă ale Spitalului Universitar Hedi Chaker din Sfax. Au fost analizate cazurile care aveau diagnosticul de DM sau PM şi neoplazie.*

Rezultate. *17 cazuri (13.5%) din pacienţii cu DM sau PM aveau asociere cu malignitate. 14 pacienţi au avut DM şi 3 pacienţi au avut PM. Raportul de sex masculin/feminin a fost de 0.3 şi media de vârstă a diagnosticului a fost la 56.5 ani. La pacienţii cu DM malignitatea a precedat miozita în 64.2% din cazuri. La pacienţii cu PM numai un pacient avea la momentul diagnosticului cancer de sân. Tratamentul a constat în corticoterapie asociat cu methotrexat la 4 pacienţi. La 5 pacienţi s-a înregistrat deces- 3 dintre acestea datorate cancerului şi 2 datorate tulburărilor de deglutiţie.*

Concluzii. *Nu s-au evidenţiat caracteristici specifice clinice sau biologice la pacienţii cu DM paraneoplazică. La pacienţii analizaţi, cancerul de sân a fost primul asociat cu DM. Cancerul nazofaringelui, colonului şi ale tractului urinar au urmat ca frecvenţă.*

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