A STUDY OF CUTANEOUS DISORDERS ASSOCIATED WITH INTERNAL MALIGNANCY

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ABSTRACT

More than 50 conditions, both malignant and benign have been cited as markers of internal malignancy. Metastases to the skin from internal tumours are uncommon, yet they may be the first presentation of such malignancies. Also, paraneoplastic dermatoses (PND) are important cutaneous markers of internal malignancies.

The present work was undertaken in an effort to evaluate the prevalence of cutaneous disorders occurring in association with internal malignant diseases, aiming at early diagnosis and therapy of various internal malignancies and improving their survival rates.

The study included 163 patients already documented as cases of internal malignant disease of various origins. All the studied cases were subjected to history taking, careful dermatological examination, some dermatological investigations when indicated (for fungus), skin biopsy for histopathological examination of skin lesions and photography.

We found a very high prevalence of cutaneous disorders in the studied cases (93.3%). Malignant skin involvement was found in 8.4% of cases (14) most commonly with cancer breast (4 cases). They developed the malignant skin involvement after the primary cancer by a highly variable duration (2 weeks, 30 months). The most frequent primary cancer was adenocarcinoma and squamous cell carcinoma.

The majority of PND appeared after the diagnosis of primary cancer

skin (metastatic and direct extension), genodermatosis, paraneoplastic dermatoses and skin manifestations of exposure to environmental carcinogens.

Paraneoplastic dermatoses are important cutaneous markers of internal malignancies. They form a hetrogenous group of skin diseases, where tumour induced immunologic factors, hormones, metabolic disorders and epidermal growth factor which may play a role in the onset of the symptoms (5).

The aim of this study was to evaluate the prevalence of cutaneous disorders occurring in association with the already diagnosed cases with internal malignancies of various origins and to evaluate the importance of the discovery of these cutaneous manifestations in the early diagnosis and therapy of internal malignancies and in improving their survival rates.

PATIENTS AND METHODS

Our Study included 163 patients already documented as cases of internal malignant disease. The patients were taken consecutively from the various inpatient sections of Mansoura University Hospitals and they were admitted mainly in pediatric, Oncology Medicine, Surgical Oncology and Radiotherapy Departments in addition to some cases were taken during a dermatological consultation in our outpatient clinic of dermatology when their files were available and containing the required investigations. The study also included a number of patients who were admitted to our department for a dermatological complaint and we were able to prove their malignant aetiology.

All patients who were included in our study were subjected to the following in their original section of admission:-

1- Good history taking: especially for the presenting complaint e.g. swelling, pain, jaundice, skin or mucosal lesion, the duration of the complaints and the age of the patient.
2- Clinical examination: with special attention for the system involved by the malignant disease and also for the clinical staging.
3- Basic laboratory investigations: as blood picture, urine, stool examination and blood sugar.
4- Radiological workup: including X-ray chest, Bone scanning to detect metastatic disease, ultrasonography, computerized scanning and other ra-

already documented as cases of internal malignant disease. They were 100 males (61.3%) and 63 females (38.7%). The most common age group was between 41-60 years old (54 patients = 33%) followed by the age group over 60 years old (43 patients = 26.4%). The age groups between 18-40 years and below 18 years old were 20.9% and 19.7% respectively.

Leukemia (41 patients = 25.2%) and lymphoma (39 patients = 23.9%) were the most frequent original cancer in the studied cases, followed by urinary bladder (18 patients = 11%), breast (12 patients = 7.4%) and liver cancers (11 patients = 6.7%), while the other types of cancers were much less frequent: rectum, lung and stomach (6 patients = 6.7%, 5 patients = 3.7% and 4 patients = 2.5% respectively). Brain, ovary, oesophagus, prostate and kidney were the origin of internal malignancy in 3 patients (1.8%) in each, colon, pancreas, larynx and bone were the origin of internal malignancy in 2 patients (1.2%) in each. Thymus, thyroid, testis and soft tissue were the origin of internal malignancy in 1 patient (0.6%) in each.

As regards the histopathology of the original cancers of the studied cases: carcinoma was the most frequent (34.9%) followed by leukemia (25.2%) and lymphoma (23.9%), while sarcoma and glioblastoma were much less frequent (14.7% and 1.2% respectively).

The prevalence of cutaneous disorders in the studied cases was 93.3% (152 patients showed dermatological findings) while only 11 patients (6.7%) were free form any dermatological findings.

Table (1) shows the cutaneous manifestations in patients with internal malignancy. Malignant skin involvement was encountered in 14 patients (8.4% of total patients with internal malignancy). They were 4 cases with intraduct carcinoma of the breast (out of 12 cases of cancer breast), 2 patients with lymphoma (out of 39 patients), 2 patients with hepatoma (out of 11 cases with malignant liver disease), 1 patient with leukemia, 1 patient with adenocarcinoma of the rectum, 1 with lung adenocarcinoma, 1 with adenocarcinmoma of the stomach, 1 with adenocarcinoma of the prostate and one with squamous cell carcinoma of the larynx. The clinical picture of malignant skin involvement

logic malignancy (16.6%). The commonest viral infection was herpes zoster (H.Z) (6%) followed by herpes simplex (H.S) (4.9%), then molluscum contagiosum (1.2%) (fig. 5).

Table (4) shows bacterial skin infections in the studied cases, it was the commonest in the kidney and brain tumours (33.3% of each) followed by lung tumours (20%), rectal (16.6%), breast (16.6%) then lymphoma (15.4%) and leukemia (14.3%). The commonest bacterial infection was erysiplus and folliculitis (2.4% for each) followed by erythrasma and abscesses (1.8% of each) then cellulitis (1.2%) and necrotizing fasciitis (0.6%) (fig. 6).

Table (5) shows the fungal skin infections in the studied cases, it was the commonest in cancer colon (100%) followed by brain tumours (66.6%), urinary bladder (56.6%), and stomach (50%). The commonest cutaneous fungal infections was dermatophytosis (27%) followed by candidiasis (5.5%) and the least frequent was mycetoma (0.6%) (fig. 7).

Table (6) shows vascular and blood abnormalities in patients with internal malignancies. They were the commonest in leukemia (29.3%) followed by lymphoma (12.8%) then in hepatoma (9.1%). The commonest presentation was purpura (8%) then erythema multiforme (EM), allergic vasculitis (1.2% for each) followed by disseminated intravascular coagulopathy (DIC) (0.6%).

Table (7) shows that icterus was present in 11.7% of cases with internal malignancies, pruritis was present in 6.2% of cases, prurigo in 4.3%, acquired ichthyosis in 3.1%, erythema annulare centrifugum and pyoderma gangrenosum in (1.2% for each), and dermatomyositis was present in only 0.6%. icterus and pruritis were most commonly present in hepatoma (fig. 8)

Table (8) shows chronological relationship between some dermatoses and cancers in the studied cases. Thirty percent of cases with pruritis, 14.3% of cases with prurigo and 15.8% of cases with icterus developed their skin findings before the onset of internal malignancy, while 23.1% of cases with purpura, 11.1% of cases with bacterial infections, 15% of cases with viral infections and 10.5% of cases with icterus developed their skin lesions simultaneously with the onset of internal malignancy.

Table (2): Skin infections in patients with internal malignancy

Tumour	No.	Viral inf.		Bacterial inf.		Fungal inf.		Ectoparasitic inf.	
		No.	%	No.	%	No.	%	No.	%
Leukemia	41	7	4.3	6	3.7	15	9.2	2	1.2
Lymphoma	39	7	4.3	6	3.7	12	7.4	3	1.8
U. bladder	18	0	0	0	0	10	6.1	0	0
Breast	12	2	1.2	2	1.2	3	1.8	3	1.8
Liver	11	0	0	0	0	3	1.8	0	0
Rectum	6	0	0	1	0.6	2	1.2	0	0
Lung	5	2	1.2	1	0.6	1	0.6	0	0
Stomach	4	2	1.2	0	0	2	1.2	0	0
Brain	3	0	0	1	0.6	2	1.2	0	0
Ovary	3	0	0	0	0	0	0	0	0
Oesophagus	3	0	0	0	0	1	0.6	0	0
Prostate	3	0	0	0	0	1	0.6	0	0
Kidney	3	0	0	1	0.6	0	0	0	0
Bone	2	0	0	0	0	0	0	0	0
Colon	2	0	0	0	0	2	1.2	0	0
Pancreas	2	0	0	0	0	0	0	0	0
Larynx	2	0	0	0	0	0	0	0	0
Thymus	1	0	0	0	0	0	0	0	0
Thyroid	1	0	0	0	0	0	0	0	0
Testis	1	0	0	0	0	0	0	0	0
Soft tissue	1	0	0	0	0	0	0	0	0
Total	163	20	12.3%	18	11.0%	54	33.1%	8	4.9%

Table (4): Bacterial skin infections in patients with internal malignancy

Tumour	Abscess		Cellulitis		Erysipelas		Folliculitis		Bokhart's impetigo		Erythrasma		Necrotizing fasciiitis		Total / tumour	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Kidney (no=3)	1	33.3	0	0	0	0	0	0	0	0	0	0	0	0	1	33.3%
Brain (no=3)	0	0	0	0	0	0	1	33.3	0	0	0	0	0	0	1	33.3%
Lung (no=5)	0	0	1	20	0	0	0	0	0	0	0	0	0	0	1	20%
Rectum (no=6)	1	16.6	0	0	0	0	0	0	0	0	0	0	0	0	1	16.6%
Breast (n=12)	0	0	0	0	1	8.3	0	0	0	0	1	8.3	0	0	2	16.6%
Lymph. (n=39)	1	2.6	0	0	2	5.1	2	5.1	0	0	1	2.6	0	0	6	15.4%
Leuk. (no=41)	0	0	1	2.4	1	2.4	1	2.4	1	2.4	1	2.4	1	2.4	6	14.3%
Others(no=109)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total (no=163)	3	1.8%	2	1.2%	4	2.4%	4	2.4%	1	0.6%	3	1.8%	1	0.6%	11.0%	

Table (7): Other dermatoses in relation to the type of tumour and to the total number of cases

Tumour	No.	Dermato-myositis		Pyod. gangr.		Prurigo		Pruritis		Eryth. annulare		Acquired ichthyosis		Icterus	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Leukemia	41	0	0	0	0	1	2.4	2	4.8	0	0	1	2.4	7	17.1
Lymphoma	39	0	0	1	2.6	6	15.6	2	5.2	1	2.6	2	5.2	6	15.4
Breast	12	1	8.3	1	8.3	0	0	0	0	0	0	0	0	0	0
Liver	11	0	0	0	0	0	0	5	45.5	0	0	0	0	6	54.6
Rectum	6	0	0	0	0	0	0	0	0	0	0	1	16.7	0	0
Lung	5	0	0	0	0	0	0	1	20.0	1	20.0	0	0	0	0
Colon	2	0	0	0	0	0	0	0	0	0	0	1	50.0	0	0
Others	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	163	1	0.6%	2	1.2%	7	4.3%	10	6.2%	2	1.2%	5	3.1%	19	11.7%

Fig. (1) : Paget's disease in a patient with right cancer breast (intraductal carcinoma).

Fig. (3) : Cutaneous metastases in a patient with cancer larynx (sq.c.c.).

Fig. (2) : Papulonodular metastases in a patient with right cancer breast after mammoplasty.

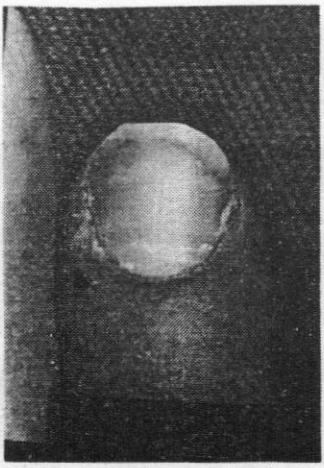

Fig. (4) : Transverse melanonychia in a patient with Hodgkin's lymphoma.

DISCUSION

More than 50 conditions, both malignant and benign, have been cited as markers of internal malignancy. A true association is readily accepted when a cutaneous metastasis coexists with a primary internal malignancy, but the relationship is not so easily proved when a benign dermatosis is linked to an underlying malignant neoplasm (4).

Curth (1976) (6), generated several criteria for determining whether a true association exists between a cutaneous disorder and an internal malignant disease. She proposed that a real association exists if (1) the dermatosis is relatively uncommon, (2) it occurs with a specific internal neoplasm, (3) the two conditions are frequently observed together (4) the onset of the disorders is concurrent, (5) the clinical course is similar. If a genetic predisposition accounts for the appearance of both conditions, the last two criteria need not be met.

The present work was undertaken in an effort to evaluate the prevalence of cutaneous disorders occurring in association with the already diagnosed cases of internal malignancies of various origins aiming at early diagnosis and therapy of various internal malignancies and improving their survival rates.

As regards the prevalence of cutaneous disorders detected in patients with internal malignant diseases, we found that they were present in 152 patients (93.3%) from the total number of studied cases (163). To our knowledge, the collective prevalence of these disorders in this category of patients was not available in any of our available references.

Metastases to the skin from internal tumours are uncommon, yet they may be the first presentation of such malignancies. They usually arise from the breast, lung and large bowel (7). It had been cited by Lookingbitt et al. (1990) (8) that cutaneous metastases are the most specific marker of internal malignancy arising as a result of direct extension or from hematogenous or lymphatic spread of neoplastic cells. It was concluded that despite of being uncommon markers, their frequency has ranged from 0.7 to 9.0%. In agreement with this report, we found that the frequency in our studied cases was 8.4%.

In our study we found that all cas-

cancer breast).

In the present study, it was found that skin metastases from adenocarcinoma of the lung presented after the primary cancer following needle aspiration of a malignant pleural effusion and occurred on the skin of the back of the chest wall as clusters of nodules. Similar descriptions were reported in other studies (12).

It was reported that skin metastases from gastric adenocarcinoma are extremely rare (7). Here, we reported a case of a patient with gastric adenocarcinoma who developed multiple skin nodules with some ulcerated and crusted nodules. The biopsy revealed metastatic adenocarcinoma.

As regards prostatic cancer, Schwartz (1995) (13) stated that it is rare to involve the skin (1% of all cases of skin metastases) and the most common sites are inguinal area, penis, lower abdomen, thighs, scalp, nose and neck. In the present study, in agreement with the previous report, we found the site of skin involvement in one case with prostatic cancer to be in the inguinal and suprapubic areas.

Reingold and Smith (1978) (14) described skin metastases from hepatomas to be rare and appears as rapidly growing firm, painless, non ulcerative, reddish bleu nodules. Our results coincide more or less with them as we found only two cases of skin metastases from hepatomas (out of 11 cases of hepatomas) with the same clinical picture and of similar clinical course.

In the present study, we detected a case of acute monocytic leukemia in an adult female patient presented with multiple brownish-bluish disseminated papulonodular lesions on the skin of her breast and abdomen. All these criteria of metastatic skin disease in leukemia were described in previous reports (15 & 16).

When considering specific skin changes in Hodgkin's disease, Philip et al. (1997) (17) concluded that they are rare ranging from 0.5% to 3.4% of cases. However, in non-Hodgkin's lymphoma reaching about 17%. In the present study, we did not report any case of Hodgkin's disease with specific skin changes (out of 13 cases of Hodgkin's lymphoma). However, we found 2 cases with non-Hodgkin's lymphoma who had malignant skin in-

troversial in another study [20].

Wilson (1972) [21] concluded that disseminated herpes zoster (H.Z) is commonly associated with underlying neoplasm mostly leukemia and lymphoma especially after chemotherapy. We found two cases with disseminated H.Z., one with cancer stomach and one with lymphoma under chemotherapy. So, despite its very low prevalence (1.2% of cases), it should be considered as a serious signs of underlying immune compromization either due to cancer or chemotherapy.

Herpes simple (H.S) infections especially when extensive, chronic or with massive ulceration are indeed associated with cancer mostly lymphoma and leukemia (22). Our results showed that 4.9% (8) of cases developed H.S., from which 4 cases developed ulcerative and hemorrhagic lesions and were cases of lymphoma and leukemia.

A variety of bacterial and fungal infections may occur with internal malignancy, particularly when the patient has a severely compromised immunity either as a result of the malignant process or therapy [23]. In the present study fungal infections were the commonest form of skin infections (33.1% of cases), mostly in the form of dermatophytoses (27%) followed by mucosal candidiasis (5.5%) and a case of eumycetoma (0.6%). Bacterial infections were a rare finding (11% of cases) most commonly in the form of erysiplus and folliculitis (2.4% for each). Most of cases were under chemotherapy, supporting the previous hypothesis that these infections are more commonly due to immunosuppressive effects of cytotoxic agents rather than the cancer itself.

Sudden onset, in adult life, of ichthyosis similar to the pattern of ichthyosis vulgaris, does appear to be associated with internal malignancy, particularly lymphoreticular. However, cases linked with solid tumours are also well documented (24). In our cases 3.1% had acquired ichthyosis mostly they were cases of leukemia and lymphoma (3 cases). However, it was also found in one patient with cancer colon and another one with cancer rectum. The eruption in all cases was localized to the legs, of sudden onset and appeared after the primary cancer.

Both dermatomyositis and polymyositis in adults may be associated

the primary cancer or to the chemotherapeutic agents used in treatment especially that the patients noticed that the condition goes in exacerbation with each cycle of chemotherapy while it goes in remission in between.

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فى ٣ر١٢٪ والاصابات البكترية فى ١١٪ والاصابات الطفيلية فى ٩ر٤٪ وقشر السمك المكتسب فى ١ر٣٪ والحمرة الحلقية فى ٢ر١٪ والغرغرينا المتقيحة فى ٢ر١٪ والالتهاب العضلى الجلدى ٦ر٪ وتلون الأظافر فى ٤ر٧٪ وتورم الأظافر فى ١ر٣٪

ولقد استخلصنا فى هذا البحث أن الاصابات الجلدية المصاحبة للأورام السرطانية يجب أن تظل فى ذاكره طبيب الأمراض الجلدية عندما يتعامل مع أى شكوى جلدية خاصة إذا كانت هناك غرابة فى الأعراض أو كانت هذه الإصابة مقاومة للعلاج التقليدى .