REVIEW ARTICLE

Cutaneous manifestations of malignant disease: A review

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Abstract

Background: *The skin is the largest and most accessible organ in the body. Internal malignancies can produce a wide range of cutaneous manifestations that are often neglected by clinicians. This review aims to increase the awareness of clinicians by highlighting the various cutaneous manifestations of common internal malignancies.*

Method: *A review composed via Medline Internet search, literature search and contributions from our experiences as well as shared experiences from colleagues over the years.*

Results: *The skin can be involved in systemic malignancy in a variety of ways: secondary spread; as part of a genetic or acquired syndrome; as a consequence of immunosupression or as paraneoplastic phenomena. The cutaneous markers of malignancy may occur before, at the same time as, or after the diagnosis of the tumour. While in some instances the skin lesion abates with the treatment of the primary tumour, relapse of a previously treated cutaneous disease can herald recurrence of the tumour.*

Conclusion: *Systemic malignancies could, and do, produce a wide range of skin manifestations that are easily seen but often neglected by clinicians. A good understanding of these features will aid prompt and appropriate diagnosis, upon which the necessary treatment could be anchored.*

Keywords: *Skin manifestations, internal malignancy.*

Introduction

Being the largest and most accessible organ in the body, the skin covers a total of 1.0 - 1.7 m^2, constituting about 15% of the total body weight [1]. The appearance of skin lesions in patients with occult or obvious malignancy is therefore of extreme importance in the detection and management of cancer [2]. Examination of the skin of patients can provide important insights into the underlying malignant processes or possible complications from cancer treatment [3]. Systemic malignancies are capable of producing a wide variety of cutaneous manifestations [4,5]. In some instances, cutaneous involvement may precede diagnosis of the underlying tumour; in other cases, it may signify widespread dissemination or relapse [6-9]. Some skin manifestations regress or even disappear completely following treatment of the primary disease. Some of the recognized ways in which the skin may get involved in systemic malignancy include the following[10]:

1. By secondary spread. This can occur by:

(a) Direct infiltration, such as cancer en cuirasse seen in carcinoma of the breast. Carcinoma of the breast may also uncommonly present with other distinct patterns such as carcinoma erysipelatoides and carcinoma telangiectaticum, both variants of inflammatory breast cancer [11].

(b) Distant cutaneous secondary e.g. skin nodules seen in prostatic carcinoma, thyroid carcinoma, soft tissue sarcomas etc.

Sister Mary Joseph's nodule (metastatic involvement of the umbilicus) is seen in gastrointestinal malignancies such as those from the stomach, large bowel, ovary and pancreas [12, 13] This sign is named after Mary Joseph, a superintendent of St. Mary's Hospital in Rochester, Minnesota, who served as the first surgical assistant to Dr W. J. Mayo [13]. She is credited with recognizing that patients with this finding had a poor prognosis.

Alopecia neoplastica may be observed in patients with metastatic tumours of the breast, lung and kidneys. The scalp appears to be a unique site that is often involved in metastasis from internal malignancy. In alopecia neoplastica, there is an area of induration associated with alopecia, which, on histology, demonstrates loss of hair follicles and the presence of cutaneous deposits of a visceral malignancy [11].

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Metastases to the skin do not typically occur in random patterns; rather, different tumours demonstrate characteristic patterns of metastases [11]. As a rule, cutaneous metastases usually appear in the skin that is near the primary tumour. Most regional metastases are probably through the lymphatic system, while distant metastases are more likely to occur via the haematogenous route [11].

2. As part of a genetic disorder with a cutaneous component in which there is an inherited predisposition to the later development of malignancy, e.g. Tylosis.
3. As part of an acquired syndrome due to the toxicity of a carcinogen that induces malignant change and accompanying cutaneous changes e.g. vinyl chloride, causing angiosarcoma and scleroderma.
4. As a consequence of immunossupression e.g. herpes zoster in patients with lymphoma.
5. By the development of specific dermatoses that occur as paraneoplastic phenomena e.g. pyoderma gangrenosum in multiple myeloma.

Leukaemia and lymphoma are common problems in Africa, especially in children[14]. Studies done in Western populations indicate that 25-50% of patients with leukaemia and lymphomas have specific or nonspecific cutaneous signs [14]; in dark-skinned patients, reports of such mucocutaneous manifestations are scarce. The lesions in these patients could easily be missed, if not specifically looked for. In recent years, especially with the advent of acquired immunodeficiency syndrome (AIDS), new skin disorders associated with systemic diseases (including malignancies) have been described in the literature15. Paraneoplastic pemphigus, a recently characterized autoimmune vesicular eruption, produces painful mucocutaneous ulcerations in patients with occult neoplasms, such as chronic lymphocytic leukaemia or malignant lymphoma[15]. Clinical diagnosis can be difficult because of ignorance, the wide spectrum of appearance of these lesions, and, in many cases, because of the lack of an identifiable primary [9]. This review highlights some of the skin manifestations seen in common internal malignancies; in order to draw the attention of clinicians to these easily accessible but often neglected lesions. Particular emphasis is laid on some of the known biological mechanisms of tumour invasion and metastasis.

A. Cutaneous involvement in disseminated malignancy

1. Cutaneous secondaries

The skin is a relatively uncommon site for secondary deposits, cutaneous metastases only occurring in an estimated 4% of patients with malignancy [8]. However, occasionally a cutaneous secondary is the presenting feature of the primary tumour [10 12]. Significant number of cutaneous involvement results from disseminated malignancies of the gastrointestinal system, especially gastric and colonic carcinomas. While evaluating acanthosis nigricans in the late 1950s, Helen Curth arrived at five criteria that establish an association between a skin disease and an internal malignancy [16]. These criteria are called Curth's postulates:

1. Concurrent onset of the cutaneous disease and internal malignancy; or at the time of onset of the cutaneous disease, the internal malignancy is recognizable.

2. Parallel course of the skin disease and internal malignancy.

3. There is a specific type or site of malignancy associated with the skin disease.

4. Sound statistical evidence that the malignancy is more frequent in patients with the skin disease than in age- and sex-matched controls.

5. A genetic link between a syndrome with skin manifestations and an internal malignancy.

Cutaneous secondary may occur as a direct infiltration or as a distant cutaneous deposit [10, 12] (figures 1 and 2). In the past two decades, significant advances in establishing the underlying biological mechanisms of tumour invasion and metastasis have been made. The metastatic spread of cancer is a complex process that involves separate steps, the so-called 'metastatic cascade' [17]. In this process, a tumour cell undergoes detachment from the primary tumour, migrates through the basement membrane and extracellular matrix, intravasates and travels in the circulation to the new site, before reattachment, extravasation, the development of a new focus and neovascularization [18-22]. This process is initiated by motogens, a new term proposed by Stoker and Gherardi [23] but previously known as motility factors. Motogens can stimulate various aspects of tumour cell motility including migration, chemotaxis, chemokinesis, phagokinetics and hepatotaxis [17].

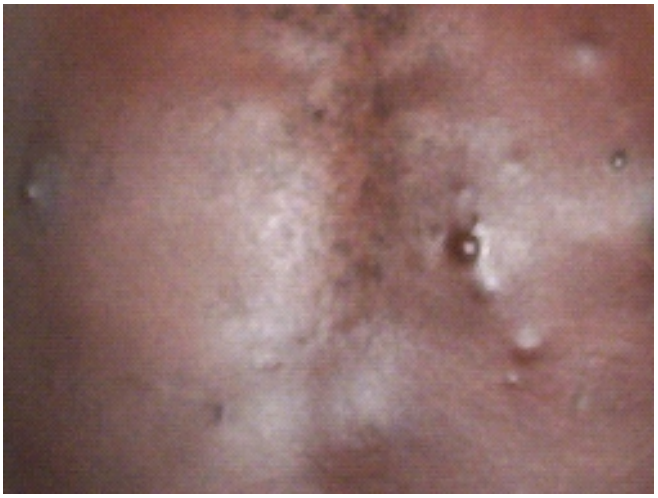

Figure 1: Cutaneous nodules in a middle-aged man with advanced carcinoma of the left breast.

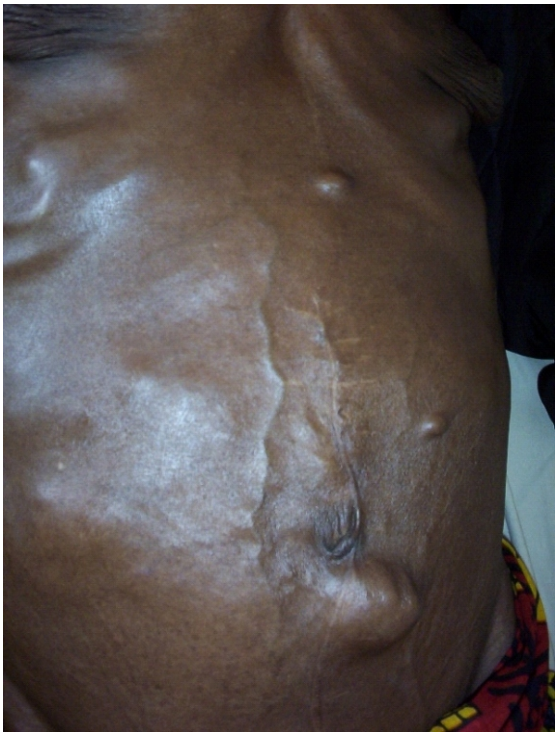

Figure 2: An elderly woman with cutaneous nodules on the anterior abdominal wall from an abdominal malignancy. Note a midline abdominal scar from previous laparotomy.

Adhesion molecules represent a group of cell surface structures that are involved in cell-to-cell and cell-to-matrix interactions [17]. They are grouped into four superfamilies: the integrins, cadherins, immunoglobulins and other adhesion molecules like selectins. The loss, dysfunction or overexpression of these molecules may promote tumour cell dissociation from primary sites and enhance their invasive nature [24-26]. The extracellular matrix is the first barrier that tumour cells encounter during metastasis. Tumour cells may produce a number of proteolytic enzymes (metalloproteinases/collagenases, plasmin, heparanases, urokinase, cathepsins tumour-associated trypsinogen and plasminogen activator) that degrade the matrix and ease tumour cell migration [27]. Matrix degradation depends on the balance between proteinases and their inhibitors. Some of the metastatic suppressor genes (e.g. nm 23) have for long been identified [28, 29]. Their expression correlates inversely with metastatic potential.

2. Adult T-cell leukaemia/lymphoma

Otherwise known as human T-cell lymphotropic virus 1 (HTLV-1)-associated disease, this tumour is emerging as a malignancy of increasing importance. The acute form of the disease is characterized in 50% of cases by the development of widespread monomorphic papular skin eruption, which represents cutaneous infiltration by lymphoma [30]. Nodular skin deposits may be observed in advanced disease. In the chronic form of the disease, skin manifestation may take a very long time to notice [31].

B. Skin involvement in haematological paraneoplastic malignancy

1. Vasculitis

Vasculitis is characterized by inflammatory changes and necrosis of blood vessels. Primary and secondary forms of vasculitis exist [32]. Secondary vasculitis has been linked to several processes, including infections, drugs, and allergic, rheumatologic and neoplastic disease (including a number of malignancies). The majority of patients with malignant neoplasm-associated vasculitis who have been described had haematologic problems[32, 33]. Its close relationship with myelodysplastic syndrome has been noted for close to two decades [33, 34]. The presence of vasculitis signifies the transformation of myelodysplasia to acute leukaemia [34]. However, cutaneous leukocytoclastic vasculitis, and other forms of vasculitis have also been reported in association with solid tumours like adenocarcinoma of the colon [34].

2. Pyoderma gangrenosum

This is a progressive necrosis of the skin and underlying tissues that is associated with leukaemias, polycytaemia vera, lymphoma, multiple myeloma and other gammopathies. The disease is of unknown

aetiology [16], but there is a direct relationship between the level of paraprotein and activity of pyoderma gangrenosum, explaining an immunological relationship [35]. The disease is associated with internal malignancy in 7.2% of patients[16], although it may also be associated with benign conditions such as inflammatory bowel disease and rheumatoid arthritis. There are rare reports of pyoderma gangrenosum associated with solid tumours.

3. Acute febrile neutrophilic dermatitis (Sweet's syndrome)

As the name implies, the disease is characterized by fever, neutrophilia and the appearance of violaceous, erythematous and indurated skin nodules or plaques which are often multiple and asymmetrical [10,35,36]. On histology, the lesions characteristically show a dense dermal neutrophilic infiltrate. Like vasculitis, Sweet's syndrome may be the presenting feature of myelodysplasia and can also herald its transformation to acute leukaemia [37]. Sweet's syndrome has a strong association with both solid tumours and haematological malignancies [38, 39]. Although the syndrome may occur in isolation, its development calls for thorough assessment.

4. Acquired ichthyosis

This presents as a dry, rough, scaly and pruritic skin condition which may be congenital. However, the acquired form is frequently associated with lymphoproliferative (e.g. Hodgkin's) and less frequently with non-lymphoproliferative malignancies [40].

C. Skin involvement in solid paraneoplastic tumours

1. Exfoliative dermatitis

This is a non-specific erythroderma which occurs in a wide range of conditions including psoriasis, eczema and ingestion of drugs or contact with chemicals. It commonly occurs with lymphoma. Its importance lies in its association with paraneoplastic syndrome (e.g. squamous cell carcinoma of the lung) when it may be found in the elderly and occurs suddenly [10].

2. Paget's disease

This occurs most commonly on the female breast, although cases have been reported in men. Paget's disease of the nipple-areola complex is an eczematous superficial manifestation of an underlying intraduct carcinoma of the breast [8, 41]. It presents as an eczema-like condition of the nipple, which gradually spreads unto the areola and eventually to the skin of the breast, persisting despite local treatment. The nipple is eroded slowly and eventually disappears. The borders of the lesion are sharply marginated, and the surface may be crusted, moist, erythematous, and/or scaly [16]. Microscopically, it is characterized by the presence of large, ovoid (Pagetoid) cells with abundant, clear, pale-staining cytoplasm in the malpigian layer of the epidermis. On rare occasions, extarmammary Paget's disease may occur on the axilla, groin, or anogenital skin. It is often associated with an underlying adnexal carcinoma, and about 20% of cases have carcinoma of the rectum or genitourinary tract [10, 16].

3. Generalized pruritus

Though non-specific and may occur in a wide variety of conditions lincluding old age, generalized pruritus may be a marker of internal malignancy; such as solid tumours (e.g. lung cancer) or reticuloendothelial malignancy [10].

4. Acanthosis nigricans

It is a dark, velvety-warty thickening of the epidermis affecting mainly the axilla, groin and mouth, although it could become generalized [16]. Originally described in association with malignancy, it could occur in a wide variety of conditions such as obesity (pseudo-acanthosis), insulin resistance and other endocrinopathies [10, 16]. Sudden onset, palmer skin involvement, accompanying oral mucosal changes and occurrence latter in life are all features of malignant acanthosis. The tumour is thought to secret a protein which stimulates epidermal proliferation [42]. It could be associated with squamous and haematological malignancies, though more frequently described in adenocarcinomas (especially gastric cancer) [43] and may precede the diagnosis in up to 20% of cases [44]. When the cancer is in remission, paraneoplastic acanthosis nigricans will remit, and if the cancer recurs, it also returns.

5. Sign of Leser-Trelat (eruptive seborrheic keratoses)

Named after the two European surgeons who first observed it, this is a rapid eruption of numerous seborrheoic keratoses of rare occurrence. It is thought to be an extension of acanthosis nigricans, which it is frequently associated with [16, 42]. Seborrheic keratoses are common in older patients, and so are cancers. The association between this skin lesion and cancer remains controversial [16].

6. Erythema gyratum repens

This is a rare but specific marker of internal malignancy which can predate the diagnosis of malignancy in 80% of cases 10. The skin rashes appear as highly pruritic, dynamic, enlarging and merging concentric rings found mainly on the trunk and giving a characteristic wood-grain appearance [10, 16]. It was first reported in conjunction with breast cancer, which remains the most common association, but has also been reported with lung, bladder, cervical and prostate cancers. The lesions usually resolve following treatment of the primary tumour and recur if the cancer returns [16,45,47].

7. Dermatomyositis

This is a skin lesion either of an autoimmune origin (in children) or associated with underlying malignancy (in adults) [47]. It comprises of a triad of:

a. Purple macular eruptions often starting from the periorbital region (heliotrope sign). In addition to the facial rash, lesions on the scalp, neck, upper trunk and extensor extremities are common.
b. Proximal myopathy, though a few patients may never develop this.
c. Either elevated serum creatinine kinase or abnormal electromyelogram.

In neoplastic as opposed to autoimmune dermatomyositis, the skin features tend to predominate over myositis. The true incidence of malignancy associated with this lesion is difficult to define. In a study of 153 patients with dermatomyositis, an associated malignancy was found in 8.5% of the total and 19.2% of the men 16; although some literature report up to 37%. It is often associated with oropharyngeal and gynaecological malignancies [48]. Most of the reported cases have been in patients over 40 years of age, but cases in children have also been reported.

8. Necrolytic migratory erythema

This is an erosive erythema most prominent at the perioral and perianal areas and very specific for an alpha cell tumour of the islet cells of the pancreas [16]. The rash, which follows a remitting and relapsing course, is frequently accompanied by severe stomatitis, alopecia, glossitis, nail dystrophy, anaemia, diabetes and diarrhea [10]. The eruptions tend to migrate and desquamate, and most patients have elevated serum glucagon levels (glucanoma syndrome). Skin biopsy shows superficial epidermal necrosis, which is usually diagnostic. Improvement of the skin lesions may be noticed following surgical excision or treatment with streptozotocin [49].

9. Porphyria cutanea tarda

This is characterized by skin fragility and bullae on light-exposed skin and heals usually with noticeable scarring. It can develop as a true paraneoplastic syndrome as a result of porphyrin secretion by the tumour, usually hepatoma and prostatic cancer [10]. Most of the patients with the skin lesions from hepatomas have also had cirrhosis of the liver. The condition (skin lesion) may also be complicated with hepatocellular carcinoma.

10. Migratory superficial thrombophlebitis

This presents as crops of oval to linear, erythematous, tender skin lesions seen most commonly on the trunk and limbs. Trousseau's sign consists of recurrent migratory superficial thrombophlebitis [16]. It commonly affects both large and small cutaneous veins, although thrombosis of internal veins can also occur. The most common associated malignancies are those of the pancreas and lungs.

Superficial migratory thrombophlebitis can also be seen in benign conditions such as Behcet's syndrome and several coagulation factor deficiencies, including deficiencies of factor XII, antithrombin III, protein S and C, plasminogen activating factor, and in hypercoagulable states as in liver/renal disease, pregnancy, infection and oral contraceptive use.

Conclusions

Internal malignancies produce cutaneous lesions that are often missed due to ignorance, the wide spectrum of appearance of the lesions, or due to lack of an identifiable underlying primary. Diagnosis of the primary internal malignancy, therefore, requires familiarity with the morphologic appearance of the cutaneous lesion.

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