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UNUSUAL GRANULOMAS OF THE SKIN SEEN IN LEBANON

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Abstract. Three unusual granulomatous diseases encountered during the past year in this Medical Center are reported: Systemic Candidiasis, Blastomycosis and sea-urchin sarcoidal granuloma. Diagnostic procedures and epidemiological significance are discussed.

Granulomatous diseases of the skin form about 1% of skin disorders seen at this medical centre (5). In 70–80% of these, the specific diagnosis can be made: Leishmaniasis, tuberculosis, sarcoidosis etc., while in 20–30% no etiological factor can be identified in spite of a reasonably thorough investigation. During the past year, we have encountered three types of granuloma rarely seen in this part of the world. Two of these are fungal: systemic candidiasis and American Blastomycosis, and the third a sarcoidal-type granuloma due to sea-urchin.

CASE REPORTS

Case 1

A 56-year-old retired army officer had proven chronic, myelogenous leukemia and was maintained on Myleran. One month prior to admission he developed fever, followed a few days later by skin lesions that appeared as erythematous papules over the hands, thighs and shins bilaterally. The nodules over the hands enlarged by peripheral extension and fused to form crusted plaques with minimal discharge. Physical examination revealed a sick-looking dehydrated man with a blood pressure of 110/70, pulse 105/min, temperature 39.3°C. Over the dorsal aspect of both hands there were sharply demarcated, elevated, firm non-tender erythematous plaques. Their surface was verrucose and crusted (Fig. 1). Over the lower extremities there were multiple, discrete, firm brownish-red papules and nodules, measuring 5–10 mm in diameter. The tongue and buccal mucosa were covered by thick adherent whitish patches. The perianal skin was erythematous and edematous. He had marked hepatosplenomegaly and palpable axillary lymph nodes bilaterally. Laboratory findings revealed a hemoglobin of 11.7 g%, hematocrit 35%, a total WBC count of 4 800/mm³ with a differential of 25% neutrophils, 38% lymphocytes, 30% blast cells, 6% myelocytes, and 1% metamyelocytes. Erythrocyte sedimentation rate was 60 mm during the first hour. The platelet count was 32 000/mm³. Urinalysis showed a trace of protein and 6–8 red cells per high power field. Twenty-four-hour urine protein determination was 0.25 g/l. The following blood tests were within normal limits: fasting blood sugar (F.B.S.), urea nitrogen (B.U.N.) uric acid, serum proteins, creatinine, cholesterol, alkaline phosphatase, bilirubin and serum transaminases. A throat culture grew yeast-like fungi and normal bacterial flora. X-rays of the chest showed a diffuse ill-defined tiny nodular pattern throughout both lung fields, sparing the periphery. The bone marrow picture was consistent with acute blastic leukemia.

Multiple biopsies were taken from the plaques over the hands and from the nodular lesions over the lower extremities. They all showed essentially similar histological findings. The epidermis displayed hyperkeratosis, focal parakeratosis with crusting, marked acanthosis and intraepidermal micro-abscesses (Fig. 2). These contained lymphocytes, neutrophils, some histiocytes and several filamentous hyphal elements, as well as small round thick-walled structures, some of which showed budding forms (Figs. 3 and 4). The filaments took the special stains for fungi. A mild chronic inflammatory cell infiltrate was seen in the upper dermis. Cultures from biopsy tissue material on Sabourauds dextrose agar did not yield any pathogens.

While in Hospital, the patient continued to have daily spiking fever. Repeated blood and urine cultures were negative. Because of the clinical picture and the histopathological findings, systemic Candidiasis was suspected and the patient was started on intravenous Amphotericin B. This was complicated by a severe shaking chill and hypotension that necessitated discontinuation of the drug. His condition deteriorated and he died in shock 34 days after admission. Post-mortem examination was not made.

Comment

Generalized systemic Candidiasis is a potentially fatal disease. The diagnosis is usually made post-mortem, probably because of the unawareness

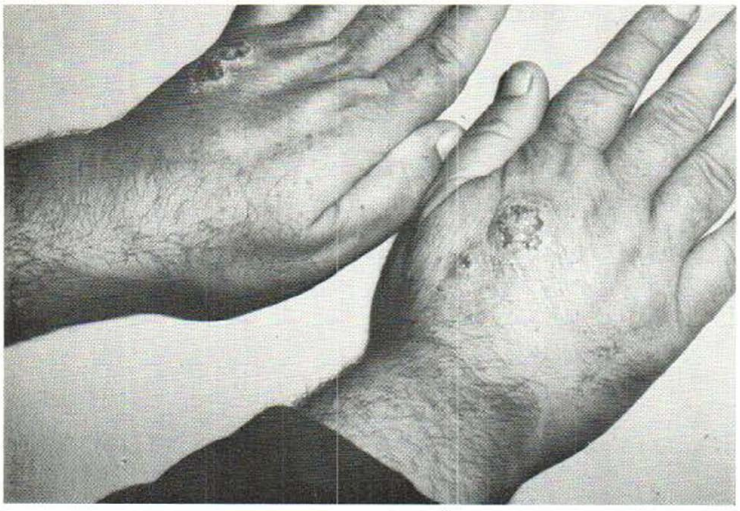

Fig. 1. Case 1. Verrucose and crusted plaques over the dorsal aspect of the hands.

by physicians of this condition and the lack of definite diagnostic clinical criteria. It is now well recognized (3, 4, 8) that systemic Candidiasis usually develops in patients suffering from certain underlying illnesses such as neoplastic diseases (notably leukemia) and diabetes mellitus; in debilitated individuals following operative procedures such as open heart surgery; or in patients who are on long-term therapy with antibiotics, steroids, immunosuppressive drugs or combinations of these. Such predisposed individuals seem to have a lowered resistance to invasion by Candidal species. This may be related to a deficiency of an anti-Candidal serum factor, as in leukemias and lymphomas. Of interest is the observation that patients with chronic leukemia have normal Candidal inhibition by their sera except in the terminal stages where this inhibitory effect falls to the level observed in patients with acute leukemia (15).

Awareness of this complication is of paramount importance for early diagnosis and treatment which can be life saving. Diagnosis rests on cultures on appropriate media of blood or fluid aspirates from body cavities or tissue biopsy material, as well as histopathological examination. The value of serological tests as an aid in diagnosis is still not well established. Recently, Taschdjian and co-workers (16) described a precipitin test using the sera of patients suspected of

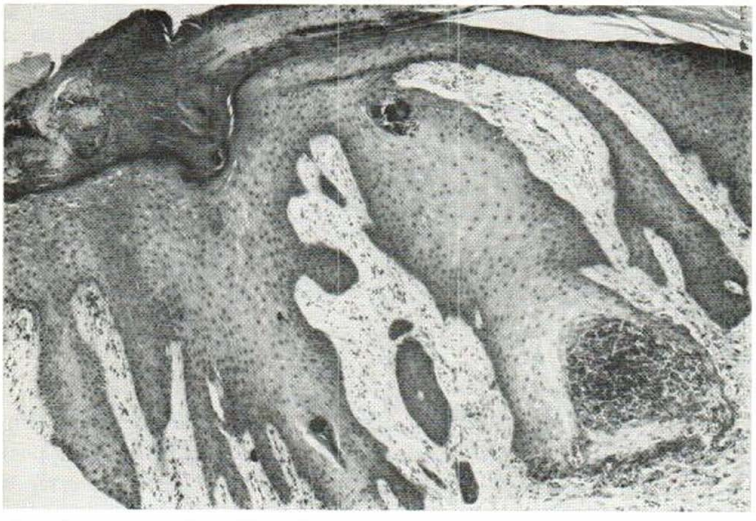

Fig. 2. Case 1. Marked irregular acanthosis of the epidermis with intra-epidermal abscess formation. Hematoxylin-eosin, × 28.

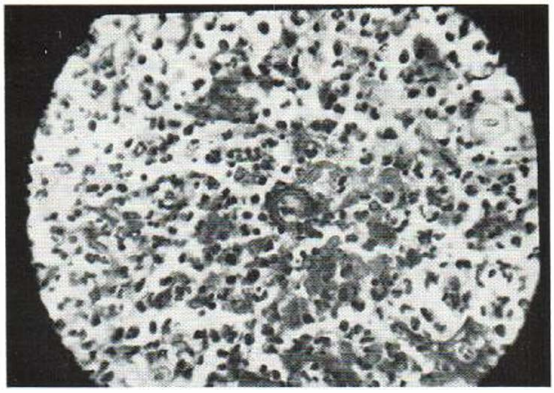

Fig. 3. Case 1. Higher magnification of an intra-epidermal micro-abscess showing thick-walled filamentous structures within an inflammatory infiltrate. Hematoxylin-eosin, × 330.

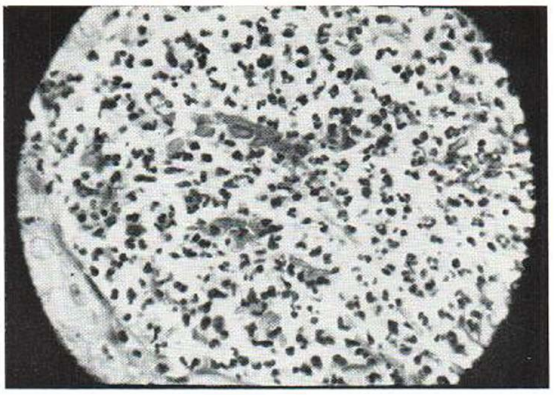

Fig. 4. Case 1. Intra-epidermal micro-abscess showing hyphal filaments and budding forms. Hematoxylin-eosin, × 330.

having systemic Candidiasis and a cytoplasmic sonicate of C. albicans, the so-called "S" antigen. Precipitins were demonstrated during life in 85% of patients with post-mortem evidence of systemic Candidiasis, whereas only 50% of these had yielded Candida in blood cultures (17). In another report of a series of 23 patients with leukemia and secondary disseminated Candidiasis, Preisler et al. (12) demonstrated precipitins using a method similar to that described by Taschdjian et al. in only 4 patients (17.4%). Thus the diagnostic value of the precipitin test has to await further confirmation. The titres of these precipitins are usually low and do not correlate with the degree and extent of the infection.

Case 2

A 46-year-old Lebanese farmer was born in Brazil but had remained in Lebanon for the past 20 years. Seven months prior to admission he developed a painless erythematous nodule over the back followed by similar lesions over the hands and face. Four months later, nodular swellings developed in the left submandibular area. On physical examination, he had multiple, large tender masses in the left submandibular and parotid areas. Some were confluent and adherent to the overlying skin. On the face, back, left palm and soles, there were annular, elevated erythematous verrucous crusted plaques, varying between 1 and 3 cm in diameter. The mouth and oral mucosa were free. The rest of the physical examination was negative. Laboratory findings including a hemogram, BUN, serum proteins, FBS, serum cholesterol and urinalysis were within normal limits. His erythrocyte sedimentation rate was 80 mm during the first hour. Liver and kidney function tests were normal. A sputum culture grew normal flora. Indirect hemmagglutination test for

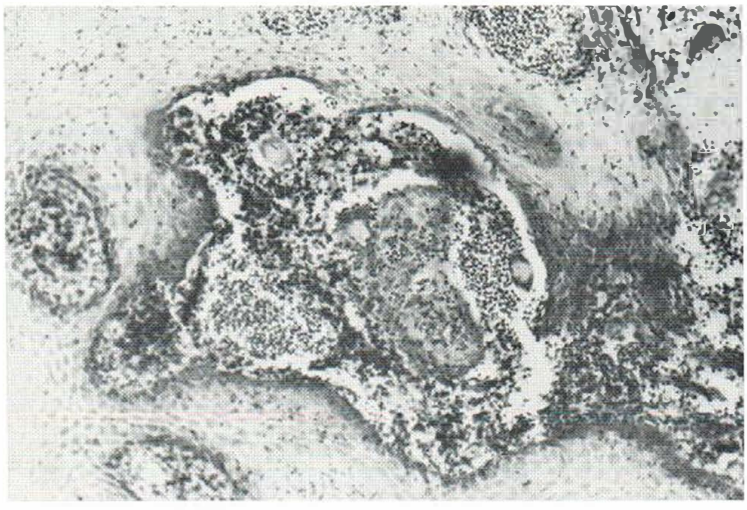

Fig. 5. Case 2. Marked epidermal hyperplasia with multiple intra-epidermal abscesses containing neutrophils and giant cells. Hematoxylin-eosin, × 100.

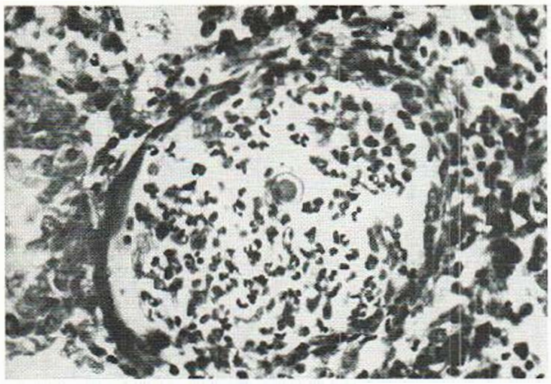

Fig. 6. Case 2. A large thick-walled spore in an intra-epidermal micro-abscess. Hematoxylin-eosin, × 330.

hydatid disease, PPD and VDRL were negative. A chest X-ray showed fibrosis in both mid-lung fields laterally. Tomographic cuts revealed an irregular cavity in the posterior segment of the left upper lobe. An intravenous pyelogram showed two tiny calcific densities in the lower pole of the left kidney, within the calices. A skeletal survey was negative. Liver biopsy was normal. A biopsy of one of the cervical nodules revealed "granulation tissue with destruction of muscle fibres and an infiltrate rich in giant cells of the Langhans type, in some of which pale structures were seen. Periodic acid-Schiff and acid-fast stains revealed no organisms". Multiple skin biopsies were made. The epidermis was covered by a thick crust and exhibited marked irregular acanthosis (Fig. 5). There were multiple intra-epidermal abscesses rich in polymorphonuclear leukocytes. Large giant cells could be seen in the epidermis, as well as in the dermis, which showed focal accumulations of inflammatory infiltrates composed of lymphocytes, plasma cells, histiocytes and numerous neutrophils. The giant cells were predominantly of the Langhans type, and in many of these, round, clear, thick-walled structures were seen. There were large, double-contoured thick-walled spores (Fig. 6) in the epidermal abscesses, some of which had single buds. These were well demonstrated with the periodic acid-Schiff stain. No tubercle formation or caseation could be seen. Cultures of the biopsy material at 37°C and room temperature did not grow any organisms.

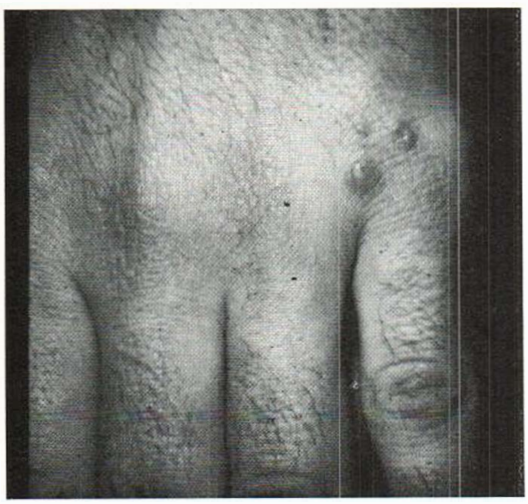

Fig. 7. Case 3. Discrete, pinkish, soft, umbilicated papules over the hand.

The patient was given a course of Amphotericin B, for a total dose of 2.5 g. Within 1 month of therapy, his lesions lost their induration. Two months later, the lesions had practically disappeared. On discharge, 85 days after admission, only slightly depressed scars could be seen. On follow-up 1 year later, he was doing well and had no evidence of activity.

Comment

In this case, it is felt that a diagnosis of North American Blastomycosis can be made, because of the clinical picture and the histological demonstration of double-contoured spores with single buds in the intra-epidermal abscesses (10). To date, none of the systemic fungal infections have been reported from the Middle East. Recently, in a survey by Malak and associates (11) of 100 Saudi Arabian patients suffering from chronic lung disease, 8 reacted positively to histoplasmin, 4 to blastomycin and 4 to coccidiodin. Previously, North American blastomycosis has been thought to exist only on the North American continent. Sporadic case reports of this disease have recently appeared from India (2), Okinawa (7) and the African continent (1). Thus the finding of North American blastomycosis in Lebanon is of obvious epidemiological significance and should focus the attention of physicians in this area on the possibility of deep fungus infections.

Case 3

A 20-year-old salesman presented with a 10 month history of asymptomatic pinkish papules over the dorsal aspect of his fingers and elbows bilaterally. He had noticed the appearance of these lesions 6 months following his last diving experience, at sites where he had been accidentally pricked by sea-urchin spines. He remembered having sustained many such injuries in the past, resulting in transient pain and discomfort followed by complete resolution. On physical examination there were multiple discrete, 2–5 mm dome-shaped papules, pinkish to violaceous in colour (Fig. 7), distributed over the dorsal aspect of the fingers and over the elbows bilaterally. Some of the papules had a central umbilication covered by a thin, loose scale. The rest of the physical examination was negative. Laboratory studies including a hemogram, urinalysis, VDRL and PPD were unrevealing.

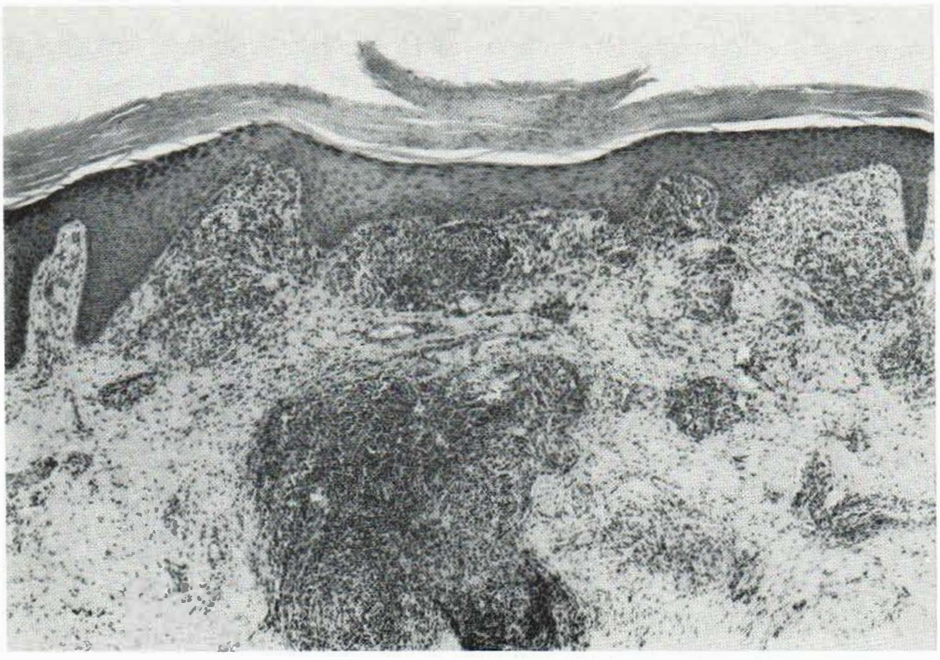

Fig. 8. Case 3. A papule showing central parakeratotic scales and a patchy dermal infiltrate. Hematoxylin-eosin, × 35.

Many lesions were biopsied. The epidermis revealed mild acanthosis with a central umbilication (Fig. 8). The underlying dermis showed well-defined granulomatous foci of epithelioid cells, histiocytes, lymphocytes and occasional giant cells of the Langhans type (Fig. 9). Some of the granulomatous foci were located superficially in the papillary dermis. There was no necrosis. Acid-fast stains did not show any organisms. Polaroscopic examination was negative. Cultures for Leishmania and atypical mycobacteria were also negative. The patient was treated with intralesional steroids with excellent response.

Comment

Sea urchins are usually found near rocky beaches. The most common Mediterranean species, *Paracentrotus lividus*, has a black body about two inches in diameter with movable, articulated spines (9). These are brittle and readily break off after penetrating the skin. Injuries caused by these spines are quite common and usually heal uneventfully over a period of 2 weeks, unless sec-

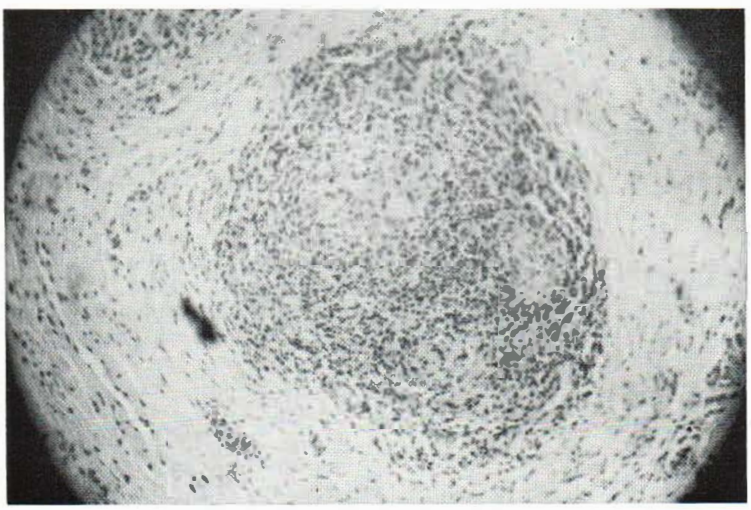

Fig. 9. Case 3. Higher magnification of one of the dermal infiltrates seen in Fig. 8 showing a granulomatous reaction made up of histiocytes, epithelioid cells and giant cells. Hematoxylin-eosin, × 100.

ondary infection sets in. Such an injury can, however, be complicated by inclusion dermoids, foreign body reactions and a peculiar delayed sarcoidal granuloma. The latter reactions usually appear after a latent period of about 2 to 6 months (14) during which time, the skin at the site of spine implantation has clinically healed, and hence can pose a considerable diagnostic problem unless the patient can recall the injury. This type of lesion must be rare, since reports in the dermatological literature are few. The first reported case was diagnosed as a papulonecrotic tuberculid (6). Temine in 1953 (18) reported similar cases and classified the lesions into papulonodular and diffuse varieties. Kinmont in 1965 (9) reported 2 additional cases and described the histological findings in the papular type, namely the presence of dermal nests of epithelioid cells and histiocytes and absence of caseation. In 1962, Rocha & Fraga (13) reported the first case in the American literature, that of a medical student who developed papular granulomata following skin diving. All the authors failed to demonstrate any foreign body or crystal fragments on polaroscopic examination. Chemical analysis of the spines showed no zirconium or beryllium (9) both of which are known to cause sarcoidal granulomas in the skin. None of the reported patients had any evidence of systemic sarcoidosis. The possibility that atypical mycobacteria can initiate such a lesion was ruled out by negative cultures and acid-fast stains.

The lesions in our patient conform to the clinical and histopathological description of the papular sarcoidal-type of sea-urchin granuloma. It was suggested by Kinmont (9) that this might represent a form of delayed hypersensitivity similar to that caused by beryllium, although Temine (18) had failed to induce a similar reaction following the experimental introduction of sea urchin spines into the skin of guinea pigs.

DISCUSSION

Throughout the world, a large number of patients suffering from chronic granulomatous diseases remain without a specific etiologic diagnosis. The 3 cases reported in this paper illustrate the fact that looking for the esoteric and rare can be rewarding and exciting. Furthermore, each of these cases focuses the attention on a different facet of the problem. Thus the concept of systemic Candidiasis has to be correlated with the underlying disease as it is evident that the "background" pathologic processes seem to be essential for the establishment of systemic Candidal infections. On the other hand, many of the deep fungus infections like blastomycosis and histoplasmosis have been associated in the medical mind with various geographic locations, mainly in the new world. Recent evidence tends to suggest that such an outlook may not be entirely correct and a world-wide distribution is more indicative of the state of affairs.

The diagnosis of sarcoidal type of granuloma due to sea-urchin rests mainly on a high index of suspicion and a rational history. It is still not clearly understood how these granulomas evolve and whether the subjects who develop such lesions have any other underlying disorder that predisposes them to the initiation of a granulomatous reaction.

It is expected that with the improvement of our diagnostic aids some of these "unknown" aspects can be explored.

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