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INTERPRETATION OF GRANULOMATOUS LESIONS IN MALIGNANCY

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In patients with malignancy the most frequent granuloma-associated conditions are tumor-related sarcoid reactions, sarcoidosis, tuberculosis and other infections. Quite often, the finding of granulomatous lesions in patients with cancer may lead to difficulties of interpretation resulting in inappropriate treatment of both granulomatous disease and malignancy. This problem is reviewed and exemplified by a number of typical case histories. A systematic diagnostic approach must integrate anamnestic, clinical, histomorphological, immunohistological and laboratory information. In addition, prolonged follow-up may be necessary in order to establish the true nature of a granuloma-associated condition.

Key words: Cancer, sarcoidosis, sarcoid reactions, granulomas.

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In patients with malignancy granulomatous lesions may quite often be fortuitous findings in primary diagnostic biopsies (1). More rarely, such lesions may be found in secondary diagnostic biopsies from previously treated patients who develop tissue changes or systemic symptoms suggesting recurrence and may, therefore, lead to further diagnostic exploration. In both situations difficulties of interpretation may lead to inappropriate treatment of both granulomatous disease and malignancy.

Although the term granuloma has been used to describe several types of circumscribed tissue changes it is reserved in this review for cases in which typical epithelioid-cell granulomas are present. Conditions in which such granulomatous lesions may occur are summarized in the Table. In some of these a local granuloma-forming process appears to be present but in others the etiologies are unknown, although various perturbations of the immune system appear to play a role (2). In the past, with few exceptions it was not possible with certainty to separate granulomatous lesions of various etiologies on morphological grounds. However, recent immunohistologic studies have revealed that at least two different families of granulomas exist: One is a B-cell negative family to which sarcoidosis and mycobacterial infection belong. The other is a B-cell positive group, comprising toxoplasmosis, tumor-related sarcoid reactions, and granulomatous lesions of unknown significance (GLUS). Importantly, this separation can be carried out retrospectively by using paraffin-embedded tissues (3).

In patients with malignant disease the most frequent causes of granulomatous lesions are tumor-related sarcoid reactions, sarcoidosis, tuberculosis, and various other infections. The other types of granuloma-associated conditions summarized in the Table are comparatively rare in these patients.

Since the etiology of some granulomatous conditions is unknown (like for example sarcoidosis) they are defined by the combination of certain symptoms and physical findings with the presence of granulomatous lesions. It is thus very difficult or even impossible to determine the underlying cause when granulomatous lesions are found fortuitously in asymptomatic patients. Nevertheless, potentially serious, but treatable, granulomatous conditions, such as sarcoidosis, and generalized infections like tuberculosis or toxoplasmosis may run a symptomless course which underscores the need for a systematic diagnostic approach, particularly in patients with malignant disease.

A short summary is given below of some important clinical features of the more frequent granuloma-associated conditions encountered in patients with malignancy.

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Table

Conditions associated with the occurrence of epithelioid-cell granulomas in various tissues

Sarcoidosis
Tumor-related sarcoid reactions
Infections (bacteria, mycobacteria, spirochaetes, viruses, fungi, protozoa, metazoa)
GLUS (granulomatous lesions of unknown significance)
Local irritants (dust particles/chemicals/skin disease)
Alimentary tract diseases (Crohn/Whipple/biliary cirrhosis)
Autoimmune diseases/immunological defects

Granuloma-associated conditions in malignancy

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. Due to this fact the diagnosis is difficult and based on the finding of non-caseating epithelioid-cell granulomas together with a typical clinico-radiographic presentation (4). The physical findings are a consequence of granulomatous or fibrotic involvement of various organ systems. In addition to immunological upsets, such as erythema nodosum, lymphopenia, hypergammaglobulinemia and anergy, a number of blood abnormalities may be present, such as hypercalcemia, and elevation of angiotensin-converting enzyme.

The granulomas of sarcoidosis are B-cell negative which distinguishes them clearly from sarcoid reactions, toxoplasmosis and GLUS, but not from the granulomas of mycobacterial infection (3). However, the granulomas of mycobacterial infection are usually—though not invariably—caseating.

Two main types of sarcoidosis may be recognised. The first is the more common self-healing subacute type with a disease duration of less than 2 years. It occurs typically in patients under the age of 30, affecting primarily the intrathoracic organs. The second is the less common chronic active type lasting more than 2 years, affecting patients over the age of 40, and involving both intra- and extrathoracic organs. As a result of chronic pulmonary changes it is associated with an excess mortality (5). Furthermore, the latter type is associated with a 5–10-fold increase of incidence of malignant lymphoma and a 2–3-fold increased incidence of lung cancer (6). Sarcoidosis may at times be associated with significant systemic symptoms like fever, malaise and weight loss, which in patients with concomitant neoplasia may wrongly be attributed to the latter condition.

The incidence and prevalence of sarcoidosis vary considerably according to age, race and location, the disease being most frequent in the 20–40 age group, among the black population in the United States, and among Scandinavians. The highest reported prevalence figure (from Sweden) is 64/100 000 (7).

Tumor-related sarcoid reactions

In individuals without any symptoms or signs of systemic sarcoidosis localized non-caseating epithelioid-cell granulomas may occur on occasion in lymph nodes draining a region housing a malignant tumor, in the primary tumor itself, and even in non-regional tissues. Thus, the definition of a sarcoid reaction requires that the patient does not have clinical features suggesting systemic sarcoidosis. Tumor-related sarcoid reactions occur with an average frequency of 4% in carcinoma, 7% in non-Hodgkin's lymphoma, and 14% in Hodgkin's disease (1). Sarcoid reactions are seen with equal frequency in primary tumors and in regional lymph nodes. In patients with carcinoma sarcoid reactions occur about 4 times more often in regional lymph nodes without metastases than in those containing tumors. Thus, sarcoid reactions in lymph nodes are not the result of a direct interaction between tumor cells and lymphoid tissue (1).

The granulomas of sarcoid reactions occurring in lymphoid tissue are B-cell positive which will distinguish them from the B-cell negative granulomas of sarcoidosis and mycobacterial infection, but not from the granulomas of toxoplasmosis and GLUS (3).

Infections

Numerous infectious agents (Table) may be associated with granulomatous lesions (2), but mycobacterial infection and toxoplasmosis are probably the two granuloma-associated infections seen most often in malignancy, and frequently they occur without any symptoms. The granulomatous lesions in mycobacterial infection are typically well-demarcated and caseating, while the granulomas of toxoplasmosis are often poorly defined microgranulomas. In addition to these histomorphological differences the granulomas of mycobacterial infection are B-cell negative, in contrast with those of toxoplasmosis which are B-cell positive (3). Morphologically the granulomas of mycobacterial infection may be confused with suppurative granulomas of cat scratch disease, while the granulomas of toxoplasmosis may be confused with proliferations of epithelioid cells which can be seen in Hodgkin's disease and Lennert's lymphoma.

Although extrapulmonary tuberculosis constitutes less than 15% of all cases (8), this variety of the disease gives rise to most diagnostic problems. Even when skin tests are positive, it may be difficult to obtain bacteriological confirmation of the diagnosis from biopsy specimens. In such cases the diagnosis of tuberculosis may hinge more or less on the finding of caseating granulomatous lesions. In the case of toxoplasmosis serologic tests for specific toxoplasma antibodies are the primary method of diagnosis, and it is usually possible to establish whether a latent or an acute infection is present (9).

Patients undergoing immuno-suppressive therapy for

malignancy may contract various types of opportunistic granuloma-associated infections, for example with fungi. However, in these cases the relationship between type of infection and the finding of granulomas is usually obvious.

Granulomatous lesions of unknown significance (GLUS)

In patients without cancer the fortuitous finding of granulomatous lesions in various sites leads to a definitive diagnosis in only 75–80% of the cases in spite of adequate diagnostic efforts (10). Accordingly the remainder of such patients must be classified as having granulomatous lesions of unknown significance (GLUS). In many patients with GLUS, monosymptomatic occurrence of localized lymphadenopathy or hepatomegaly is noted, but in some cases the condition is also associated with systemic symptoms such as fever and malaise. Although some patients may have several episodes of this kind, the course is invariably benign. It has been suggested that such cases may be due to infection with a DNA-virus, and that a special GLUS-syndrome may exist (10). Since similar cases could also occur among patients with neoplasia, it may be difficult or impossible to determine whether a granulomatous lesion in such a patient should be interpreted as a sarcoid reaction or as GLUS, especially since both types of granulomatous lesions belong to the B-cell positive family of granulomas (3).

Local irritants

Although uncommon, the occurrence of epithelioid-cell granulomas has been described in skin areas treated with local implantation of radioactive sources due to skin carcinoma and other malignancies (11). Whether such granulomas represent local tissue reactions to small treatment-induced necroses or talc granulomas (due to use of operation gloves) is unknown.

The following brief case reports illustrate some of the diagnostic difficulties and misinterpretations that may be encountered, sometimes leading to inappropriate treatment.

Illustrative case histories

Case 1. CLL was diagnosed in a 60-year-old female in whom sarcoidosis had been diagnosed one year previously. After a good remission of her CLL with chlorambucil she had intermittent pulmonary symptoms, hilar lymphadenopathy and arthritis due to her sarcoidosis. However, these symptoms were (mis)interpreted as being caused by her CLL, and she received no symptomatic treatment. Eventually her sarcoidosis healed leaving perihilar pulmonary fibrosis.

Case 2. In a 45-year-old female sarcoidosis and breast carcinoma was diagnosed simultaneously. Following primary treatment with surgery and radiotherapy she remained recurrence-free from her malignancy. The sarcoidosis proved to be of the chronic type with 2 episodes of both systemic and pulmonary symptoms occurring after 12 and 17 years respectively. After 19 years, recurrent breast cancer was suspected (but not proven) due to a gradual deterioration of her general condition with pronounced weight loss. Although sarcoidosis was the most likely cause of her poor condition, she was not offered steroid therapy.

Case 3. Sarcoidosis was diagnosed in a 31-year-old female. Subsequently, the disease healed, leaving mild pulmonary fibrosis. Eight years later a low-grade gastric lymphoma was excised. The operation appeared to be radical, but a contemporary lymphangiogram was (mis)interpreted as showing evidence of malignant lymphoma in the para-aortic lymph nodes. Accordingly, she was given 9 courses of polychemotherapy with a regimen which (unfortunately) included bleomycin. Following this treatment pronounced pulmonary fibrosis developed with dyspnoea. The patient remained recurrence-free 6 years later.

Case 4. A 62-year-old female had a hysterectomy due to a uterine adenocarcinoma, metastatic to the right ovary. One year later she was treated successfully with local radioisotopes due to a vaginal scar recurrence. At the age of 67 years she presented with a suspected malignant infiltrate in the upper lobe of the left lung. However, since lymph nodes obtained at mediastinoscopy showed epithelioid-cell granulomas and no metastases, sarcoidosis was (wrongly) diagnosed. Although treatment with a progestational drug had resulted in some regression of the lung infiltrate, this treatment was considered unnecessary and was discontinued. Following substantial growth of the lung infiltrate, adenocarcinoma was demonstrated in a needle biopsy 2 years later. However, by that time the tumor was inoperable and she died the following year with widespread cancer.

Case 5. Sarcoidosis was diagnosed in a 32-year-old female. The disease was of the chronic active type, and the patient had evidence of disease activity as late as 24 years later. At the age of 69 she had a radical mastectomy due to a breast carcinoma. The axillary lymph nodes contained several epithelioid-cell granulomas but no metastases. Immunohistological studies showed that the granulomas in the original diagnostic biopsies of sarcoidosis were B-cell negative, while the granulomas in the mastectomy specimens were B-cell positive. Thus, although she had had 'true' sarcoidosis previously, she was able to respond subsequently to the presence of a malignant tumor with a typical sarcoid reaction.

Case 6. Hodgkin's disease of mixed cellularity type was found in a single cervical lymph node in a 47-year-old male. Following local radiotherapy he was recurrence-free 22 years later. Epithelioid-cell granulomas were present in the original biopsy and were thought to represent a typical sarcoid reaction since no evidence of sarcoidosis or other

granuloma-associated conditions could be found. Nevertheless, he presented with biopsy-proven cutaneous sarcoidosis at the age of 52.

Case 7. A 51-year-old male presented with monosymptomatic swelling of the right inguinal and iliac lymph nodes. A biopsy resulted in a diagnosis of malignant lymphoma, probably Hodgkin's disease, although a national panel of pathologists disagreed about the classification of the case. No granulomatous lesions were present in the biopsy. The patient was given wide-field radiotherapy to the infra-diaphragmatic lymph nodes. Eight years later hilar lymphadenopathy and swelling of the left submandibular lymph nodes were noted. A biopsy from the latter location showed enlarged transformed germinal centers containing B-cell positive epithelioid-cell granulomas. When reviewed, the histomorphology of the primary biopsy was found to be compatible with similar non-malignant reactive changes. Since the clinical course suggested a benign chronic condition with occasional relapses, a diagnosis of GLUS was made in retrospect. No treatment was given, and the patient remained well one year later.

Discussion

The two first cases are good examples of the fact that, in a patient with a malignancy, sarcoidosis tends to be overlooked or underestimated as a cause of problems. Probably this happens particularly often in the chronic active type of sarcoidosis which is, apparently, less well known than the subacute self-healing type. Consequently, such patients are often not offered relevant symptomatic treatment.

The third case illustrates two problems: The first is that the manifestations of sarcoidosis in a patient with malignant disease (lymphangiographic changes) may be interpreted as being caused by the malignancy, and this may lead to unnecessary overtreatment of the latter disease. The second is that if pre-existing pulmonary changes due to sarcoidosis are disregarded, a type of combination chemotherapy with a pulmonary toxic potential may be chosen which may cause unnecessary additional pulmonary fibrosis.

The problem in case 4 is the reverse of that in cases 1 and 2: A malignancy is overlooked in the belief that sarcoidosis is present, and relevant treatment is withheld. This situation may occur in particular in cases in whom granulomatous lesions without tumor changes are found in lymph nodes obtained at mediastinoscopy in a patient with a pulmonary infiltrate due to lung cancer. In fact, Laurberg (12) described 3 such patients. However, in all 3 cases a subsequent thoracotomy was performed, and the correct diagnosis of lung cancer with concomitant sarcoid reaction was established. In this situation the differential diagnosis may be aided by an immunohistological study showing whether or not B-cells are present within the granulomas. If the granulomas are B-cell positive they represent a sarcoid reaction rather than sarcoidosis.

In case 5 the value of immunohistological studies is apparent, since in this case it was impossible to establish with any other method whether the granulomatous lesions found in the axillary lymph nodes at the time of the operation for breast cancer represented a tumor-related sarcoid reaction or residual chronic active sarcoidosis.

Case 6 illustrates that even in an apparent clear-cut case of a tumor-related sarcoid reaction the investigator may be deceived, and the patient may still have sarcoidosis, albeit in a presymptomatic form. Thus, it seems that immunohistologic studies should be performed even in such cases since a presumptive diagnosis of coexistent sarcoidosis may help to unravel whether subsequent symptoms might be due to malignancy or sarcoidosis. Unfortunately, the present case was seen many years ago, and the tissue sections were not available for review.

In the last case the primary histologic diagnosis was equivocal, but the appearance of the second biopsy in combination with the benign clinical course suggested that this was indeed a case of GLUS. It may be argued that the patient had a B-cell positive sarcoid reaction to his malignant lymphoma. However, since a recurrence of the latter disease was not found, it is difficult to explain why a secondary sarcoid reaction should not occur until 8 years later. Regardless of interpretation, this case demonstrates the need of a very careful evaluation and follow-up in cases of malignancy associated with granulomatous lesions.

The case histories reviewed above have been selected in order to show that the significance of granulomatous lesions occurring in neoplasia may quite often be misinterpreted in various ways, resulting in inappropriate treatment of malignant as well as granulomatous disease. Since granuloma-associated conditions constitute a very heterogeneous group of diseases it is not possible to suggest a standard set of investigations which will, eventually, lead to the correct diagnosis. However, a number of possibilities should be considered in a systematic way. Firstly, anamnestic information on sarcoidosis and granuloma-associated diseases should be obtained. As regards sarcoidosis, not all patients are aware of this diagnosis, and it may be necessary to review patient records as well as chest x-rays from previous hospital admissions. Secondly, a thorough clinical examination should focus on findings relevant to granuloma-associated disease. Thirdly, traditional histomorphological evaluation of granulomatous lesions biopsy materials should be supplemented with immunohistological studies. Thus, even in paraffin-embedded sections it is possible to separate B-cell positive from B-cell negative granulomas. Lastly, the combined information should be supplemented with relevant imaging studies, laboratory tests, serological tests and skin tests.

Even when all relevant information is obtained, the interpretation of granulomatous lesions in neoplasia will

remain difficult. Thus, it will quite often be necessary to combine traditional methods of clinical evaluation and immunohistological studies with prolonged follow-up in order to establish the true nature of a granuloma-associated condition. This circumstance reflects, of course, the chronic nature of some of the latter conditions.

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