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Systemic necrotizing granulomatous disease compatible with sarcoidosis

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ABSTRACT

An autopsy case of a systemic granulomatous inflammation is presented with differential diagnosis and a tentative final interpretation. The patient, a 31 years old male, was admitted to the hospital for shortness of breath and died within 17 days of his admission. Anatomic and laboratory investigations revealed a disease suggestive of sarcoidosis or tuberculosis, yet the final diagnosis remains open for discussion.

Key words: *Granulomatous disease, sarcoidosis, tuberculosis.*

RESUMEN

Se presenta un caso de autopsia de inflamación granulomatosa sistémica con diagnóstico diferencial y una interpretación final tentativa. Se trató de un paciente masculino de 31 años de edad, que fue admitido en el Hospital por presentar disnea y murió a los 17 días de internamiento. Las investigaciones anatómicas y de laboratorio revelaron una enfermedad sugestiva de sarcoidosis o de tuberculosis; sin embargo, el diagnóstico final queda abierto a la discusión.

Palabras clave: Enfermedad granulomatosa, sarcoidosis, tuberculosis.

INTRODUCTION

Chronic systemic granulomatous disease continues to be a challenge for differential diagnosis in the clinical diagnosis, treatment and in pathology. Even modern diagnostics using molecular techniques do not always permit a final diagnosis. We present such a case here of a systemic tuberculoid granulomatous inflammation for general discussion.

CASE REPORT

A 31 years old male patient was admitted to the hospital on 09/25/04 with complaints of shortness of breath for 2 days, fever, productive cough, sweats, chills and pedal edema. He was treated for right lower extremity cellulitis in June. The patient also had a past history of diabetes mellitus and hypertension since 18 years of age and chronic heart failure (CHF) with an ejection fraction (EF) of 35-39% in June of this year. The patient was transferred to the intensive care unit (ICU), intubated and put on a ventilator for hypoxemia due to respiratory failure. The chest X-Ray showed evidence of interstitial and alveolar infiltrates and micronodular lesions. Bone marrow biopsy showed non-caseating granulomas. The patient later also developed renal failure and his respiratory condition further deteriorated. He had finally positive blood cultures of coagulase negative staphylococcus and died clinically of septic shock 17 days after admission.

MATERIAL AND METHODS

A complete autopsy was done 2 days after the patient's death following Rokitansky's technique of or-

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gan dissection. Specimens taken for routine microscopy were prefixed in 10% neutral buffered formalin, blocked and postfixed the following day and embedded in paraffin. 5 micron sections from each tissue block were stained routinely with H&E and additional staining for special questions including reticulin stain, trichrome, Gram, PAS, Ziehl-Neelsen, rhodamin-auramin and methenamine-silver. Selected tissue samples were processed for polymerase chain reaction (PCR). Thick sections were cut from the paraffin block and sent to a reference laboratory for *Mycobacterium tuberculosis* Complex PCR, which was performed using the Amplicor MTB test (Roche Diagnostics) according to manufacturers instructions.

RESULTS

Gross findings

The gross findings are summarized in *table I*. The over-all gross features reminded at a miliary tuberculosis except that the necrotic debris in the granulomas was not really caseous and that the distribution of granulomas was somewhat unusual in so far as granulomatous spread to the liver and serosal membranes was grossly not obvious. Thus, acute progressive (necrotizing) sarcoidosis and other forms of granulomatous vasculitis needed to be considered as differential diagnosis. *Figure plate 1* shows representative gross organ changes.

Microscopic findings

All involved organs as given in table 1 including the myocardium showed necrotizing epithelioid cell granulomas with some multinucleated giant cell (*Figure plate 2*). Giant cells contained occasional asteroid bodies. Some granulomas developed adjacent to larger vessels, and severe granulomatous vasculitis with intimal fibrosis and vascular stenosis was a frequent finding in the lungs. Necrotic areas consisted of eosinophilic cellular debris (coagulation necrosis), yet no neutrophilic infiltration was seen nor caseous or fibrinoid necroses. All special stains for bacteria or fungi were negative. No parasites were found.

Some granulomas underwent fibrosis starting at their periphery with collagen fibers surrounding individual epithelioid cells and progressing to a more diffuse starry scarring. Most extensive fibrosis was noted in the myocardium and in pulmonary hilar lymph nodes. Both, the over-all composition of the granuloma as their apparent variable age did not support the diagnosis of miliary tuberculosis, and other types of necrotizing granulomatous diseases needed to be considered in differential diagnosis (see COMMENT below). There were prominent signs of calcium precipitation in renal tubular cells and in the ureters. The liver, in addition to few granulomas in the portal triads, showed extensive fatty metamorphosis of hepatocytes. Practically all glomeruli hd the most severe forms of glomerulosclerosis

Table I. Gross findings at autopsy and provisional anatomic diagnosis.

I. Systemic 'miliary type' non-caseating granulomatous disease:
   - I.1 Granulomatous infiltrates in lungs (all lobes), spleen, and kidneys.
   - I.2 Granulomatous lymphadenitis involving pulmonary hilar and paratracheal lymph nodes.
   - I.3 Focal nodular infiltrates in skin with partial ulceration, R & L tibia.
   - I.4 Severe diffuse fatty change of liver.
   - I.5 Severe diffuse fatty change and anemia of heart with suggestive focal infiltrates.
   - I.6 Large white kidneys suggestive of nephrotic syndrome and nodular infiltrates.

II. Suggestion of right heart failure:
   - II.1 Dilatation of right heart ventricle.
   - II.2 Acute congestion of liver, spleen and thyroid.

III. Moderate obesity (body weight: 274 kg):
   - III.1 Diabetes mellitus clinically.
   - III.2 Grossly unremarkable pancreas.

Primary cause of death: Systemic granulomatous disease suggestive of acute sarcoidosis (tuberculosis?).

Immediate cause of death: Cardio-respiratory failure.

besides extensive arterio-arteriolosclerosis and occasional necrotizing granuloma. Other significant organ- and tissue changes are given in the final anatomic diagnosis *(Table II)*.

PCR results

No *Mycobacterium tuberculosis* complex DNA was detected in the tissue as determined by the reference laboratory. Even though the assay used for PCR is not cleared by the FDA for use on non-respiratory samples this assay was validated for use on other specimens by the reference laboratory.

Final anatomic diagnosis

The final anatomic diagnosis is summarized in *table 2.* Besides the severe necrotizing granulomatous dis-

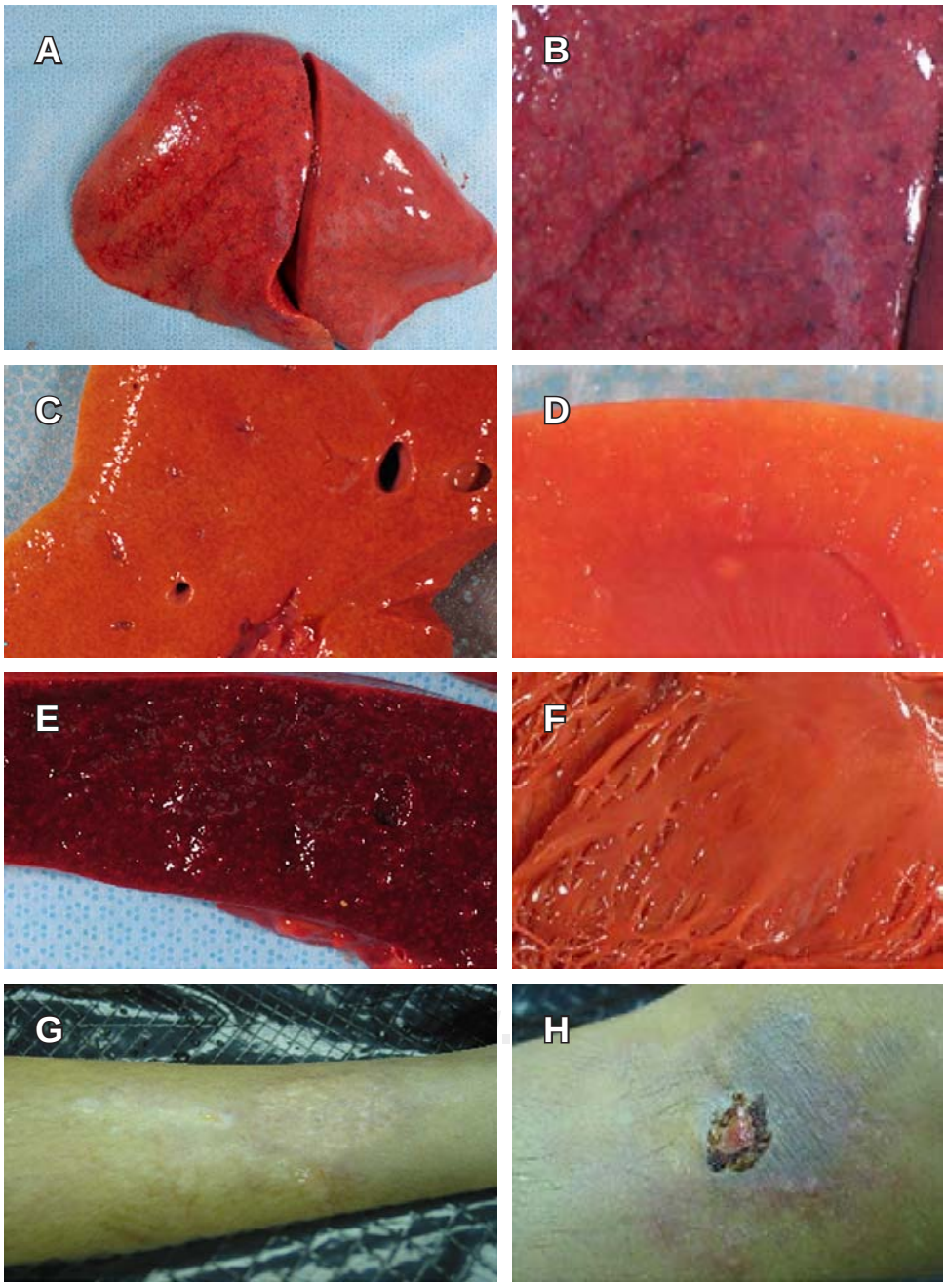

Figure plate 1. *Gross appearance of selective organs at autopsy.*

A and B: *Pale yellowish lungs with multiple small white granulomas.*
C*: Smooth soft yellowish liver w/o grossly apparent granulomas.*
D*: Swollen yellowish kidneys with effacement of cortico-medullary junction and some white granulomas.*
E*: Cut surface of spleen with multiple greyish granulomas.*
F*: Yellowish soft myocardium with focal infiltrates, R. ventricle.*
G and H: *Nodular pretibial dermal infiltrates with focal non-caseous necrosis.*

ease, other organs showed alterations as possible consequence of diabetes mellitus such as moderate obesity, severe fatty change of the liver, and extensive renal glomerular sclerosis of Kimmelstil-Wilson type. The pancreas itself was too autolytic to see any diabetic changes in the islets. The extent and the age of cardiac involvement suggests that the heart was a prime organ in this granulomatous disease, and cardiac failure may have been as well the ultimate cause of death. Hypertensive cardiomyopathy in diabetes mellitus may have further contributed to the cardiac failure.

COMMENT

Our suggestive gross diagnosis was that of a systemic sarcoidosis leading to acute death. This assumption was based upon the quality of the granulo-

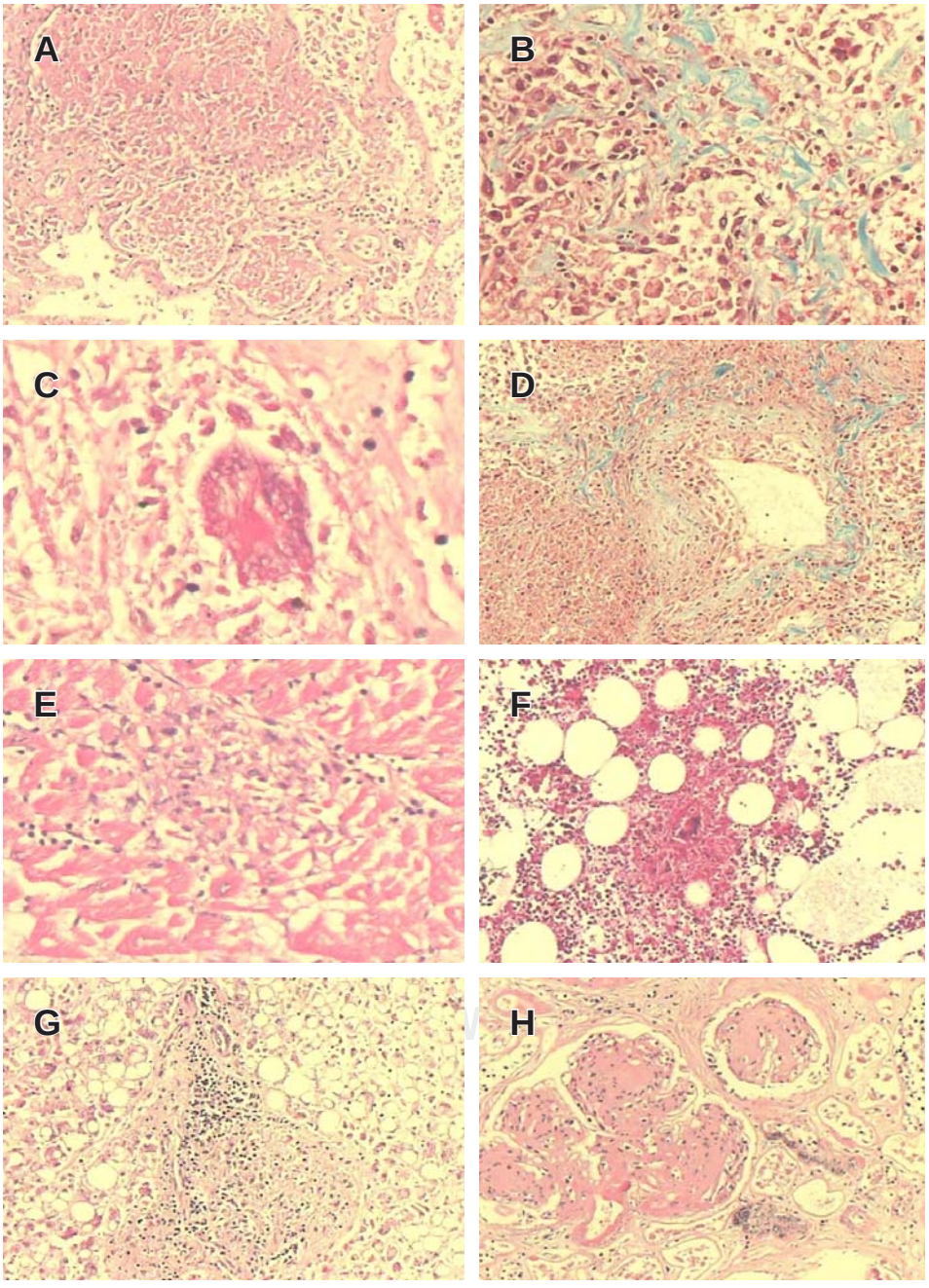

Figure plate 2. *Selected microscopic features in different organs at autopsy.*

A and B: *Pulmonary granulomas with extensive cellular coagulation necrosis and early fibrosis (H&E, 150X (**A**) and trichrome, 300X (**B**).*
C: *Typical giant cell with asteroid body (H&E,600x).*
D: *Pulmonary granuloma with vascular involvement (trichrome, 150X).*
E: *myocardial granuloma (H&E, 300X).*
F: *Bone marrow necrotizing granuloma (H&E, 150X).*
G: *Severe fatty change in liver with portal granuloma (H&E, 150X).*
H: *Severe Kimmelstil-Wilson type glomerular sclerosis and tubular cell calcification (H&E, 150X).*

Table II. Final anatomic diagnosis.

I.	Severe systemic sarcoidosis with extensive necroses.
I.1	Granulomatous infiltrates involving lungs (all lobes), spleen, liver, thyroid, bone marrow, heart and kidneys.
I.2	Granulomatous lymphadenitis involving pulmonary hilar and paratracheal lymph nodes.
I.3	Severe diffuse vacuolar degeneration of myocardial fibers and patchy interstitial fibrosis (suggestive of «healed» granulomas).
I.4	Focal tubular necrosis with calcification.
I.5	Ansarka (ascites and severe edema of lower extremities).
I.6	Prominent calcification of ureters.
II.	Suggestion of right heart failure.
II.1	Dilatation of right heart ventricle.
II.2	Acute congestion of liver, spleen and thyroid.
III.	Diabetes mellitus (clinically).
III.1	Moderate obesity (body weight: 274 kg).
III.2	Autolytic pancreas (islet cells not evaluable).
III.3	Severe fatty change of hepatocytes.
III.4	Severe glomerulosclerosis of Kimmelstil-Wilson type, arterio- arteriolosclerosis.

Primary cause of death: Systemic necrotizing sarcoidosis, diabetes mellitus.

Immediate cause of death: Cardiac failure.

mas (non-caseating) and their distribution including the kind of changes in skin and heart. Heart involvement by sarcoidosis is known to occur in up to 20% of the cases with the risk of sudden death.[4,14,15] Anular papules, scar formation and ulceration as in our case have been described in sarcoidosis.[2,16]

The prime differential diagnoses of gross findings were miliary tuberculosis or some other septic fungal infection. Rarely, systemic granulomatous reactions may accompany malignant lymphoproliferative diseases.[3]

As microscopy revealed prominent necroses in most of the granulomas, additional diagnoses had to be considered: systemic granulomatous and necrotizing vasculitis, first of all, Wegener's disease. In addition, although less probable, Churg-Strauss disease, allergic angiitis and granulomatosis or other infections such as yersiniosis and tularemia.

Special staining of various tissue specimens did not reveal organisms, neither mycobacteria, nor fungi or any other kind of bacteria. Although mycobacteria are found by microscopy in only one third of the miliary tuberculosis cases,[11] such cases show usually only non-caseating granulomas. Once prominent necroses develop (as in our patient), mycobacteria are easily detected by Ziehl-Neelsen stain or by rhodamin-auramin fluorescence. Atypical mycobacteria usually stain positive with PAS reactions. They commonly do not cause the necroses as seen in our patient, but rather histiocyte-rich granulomas. All of our PAS stains remained negative. Mycobacterial cultures and PCR are positive in most cases of miliary tuberculosis. Cultures were done in our case and showed only once (from spinal fluid) very rare acid-fast organisms. PCR from autopsy tissue samples remained negative. Thus we were rather unable to confirm the diagnosis of miliary tuberculosis.

Similarly, no fungal or bacterial organisms were demonstrated in the granulomas. Also, the composition of our patient's granulomas (epitheloid cell nodules with central non-caseous necrosis) is not characteristic for yersiniosis or tularemia which present rather histiocytic granulomas with a centrally located abscesses and prominent lymph nod involvement («abscedizing histiocytic lymphadenitis»).

Wegener's granulomatosis can show a tissue distribution quite similar to sarcoidosis[5] with involvement of lungs, kidneys, skin, nervous system and eyes, musculoskeletal system and heart. The granulomatous vasculitis in Wegener's, again is rather histiocytic than epitheloid cellular, and the type of fibrinoid vascular necrosis with some neutrophils in Wegener's is rather uncommon in sarcoidosis. Wegener's disease and it's tissue features are rather suggesting a B-cell mediated autoimmune reaction (with cANCA positivity), while sarcoidosis resembles a T-cell autoimmune response.[7]

Like in Wegener's disease, the necrosis in Churg-Strauss disease (CSD) differs from that of sarcoidosis. It is a collagenolytic (fibrinoid) necrosis as op-

Table III. Organ and tissue distribution in systemic sarcoidosis.

Organ site	*Frequency (%) of involvement*[1]	*Our case*
Lungs	> 90	+
Lymph nodes	90	+
Spleen	80-90	+
Musculoskeletal system	20-30	?
Skin	20-35	+
Eyes	20-80	?
Liver	20	+
Kidney	10-20	+
Heart	5-20	+
Neurologic	2-7	?

[1] From (1,5,14,15)

posed to the cellular necrosis in sarcoidosis and shows focal accumulations of histiocytes and eosinophils, yet no classical epitheloid cells.[9] Vasculitis also shows typical fibrinoid necroses of the vessel wall. The clinical presentation of CSD usually includes a history of asthma and eosiniphilia.[6] No such history, nor fibrinoid necrosis or vasculitis were present in our case. Similar criteria apply to other forms of systemic vasculitis, although occasionally sarcoidois can be complicated by vasculitis.[7,8]

Thus sarcoidosis — *per exclusionem* — appears the most reasonable diagnosis in our patient, and typical asteroid bodies were noted in occasional giant cell *(Figure plate 2).* Unfortunately, the patient died before additional clinical tests could further confirm this diagnosis. The rapid downhill clinical course with his sudden demise as well as the prominent necroses in pathological lesions were initially felt untypical for sarcoidosis and rather suggesting miliary tuberculosis or even septic yersiniosis. Necrotizing forms of sarcoidosis have repeatedly been described,[12] however, and sudden death is well known in patients with cardiac involvement[4,15] as well as of renal failure,[1] both occurred in our case. Finally, the organ distributions of granulomatous sarcoid lesions in our patient compares well to respective reports in the literature[10,13,14] *(Table III*).

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