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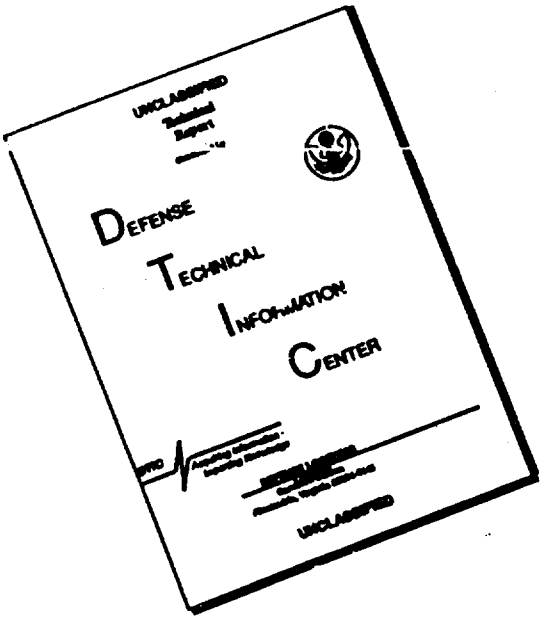

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CLINICAL ASPECTS OF COCCIDIOIDOMYCOSIS

CLINICAL ASPECTS OF COCCIDIOIDOMYCOSIS[1]

[Following is a translation of an article by K. Klutsch, N. Hummer, H. Braun and A. Heidland, from the clinic of the Medical University, Wurzburg (Director: Professor Dr. E. Wollheim), in the German-language journal Deutsche Medizinische Wochenschrift 90:1489-1501, August 27, 1965, pp 1498-1501.]

In June, 1964 there appeared in a German professional journal for lung therapeutics an article entitled "Coccidioidomycosis in Germany?", in which in view of trans-Atlantic travel attention was called to the possibility of such an infection in Germany.[21] At that time there were already in our clinic two patients with a coccidioidomycosis which as a clinical picture hitherto unknown to us provided a diagnostic and therapeutic problem about which the following should be related.

Casuistics

Case 1: A 38-year old mycologist fallen ill on February 1, 1964 with febrile difficulty in breathing, and pains in the head and limbs. At home under the assumption of a virus infection, it was first treated with penicillin then with tetracycline. After a transitory cessation of fever on Feburary 13, 1964, a pulmonary recurrence of fever with acute symptoms set in which was suspiciously diagnosed as a protracted viral pneumonia and led to hospitalization.

The admittance finding on February 20, 1964 was temperature elevated to 37.8° axillary, tachycardia at 100/min, marked dyspnea and tachypnea as well as irritative cough

[1] On the 65th birthday of Professor Dr. E. Wollheim.

with expectoration of a whitish foamy sputum. Bronchovesicular respiration was found by auscultation over both middle-upper fields with sporadic consonating rales. The blood picture showed leucocytosis of 10,800 with displacement to the left corresponding to 8% rod nuclei, 66% segment nuclei, 2% eosinophils, 20% lymphocytes, 4% monocytes, sedimentation speed at 78/112 mm. The chest X-rays showed on February 26, 1964 confluent pneumonic infiltrations in the left middle-upper field and right lower field with pleural changes in the right diaphragm and enlargement of the hilus gland (Figure 1)*. Since the patient was mycologically exposed four weeks before the start of his disease on January 2, 1964, in differentiating a hyphomycetes culture in the skin lesion of a U.S.-soldier as Coccidioides immites, a fungus pneumonia was presumed in him as well.[32]

The sputum in microscopic examination on February 26, 1964 showed fungi of the type of Coccidioides immites, whose demonstration was successful in beerwort nutrient medium and also in guinea pig innoculation experiments (Institute for Hygiene and Microbiology at the University of Wurzburg, Director: Professor Dr. C. Sonnenschein).

The skin reaction to coccidioides gave a twofold positive on February 26, 1964, a complement fixation titer 1:32 of coccidioidomycocis was found in the serum (Walter Reed Army Medical Center).

From the start the patient showed as the most severe general symptoms with remarkable numbness, increasing tachycardia, considerable dyspnea and tachnypnea, so that initially the question of a dissemination was discussed. Despite cessation of fever on the eighth day of treatment the pleuropneumonic finding remained unchanged for four weeks with increasing weight loss, persistent coughing and continuous expectoration of coccidioides immites, the condition became so much worse that the question of amphotericin-β-therapy was frequently raised. In the blood picture on February 24, 1964 a fleeting eosinophilia occurred to an 8% maximum. The complement fixation test on March 5, 1965 remained constant at a titer of 1:32 coccidioidomycocis. The pulmonary findings subsequently slowly regressed without specific therapy within another four weeks under normalization of the blood picture and sedimentation rate of the blood corpuscles. The final chest X-ray examination on July 1, 1964 gave pleural deposits over the left middle field and pleural adhesions in the right diaphragm (Figure 2). In a control examination on December 17, 1964, Coccidioides immites was still demonstrable in the sputum of the patient. The X-ray control then

*[Figures not included in this report.]

still gave streaked pleural deposits over the left middle field and a diaphragmatic point right pericardically.

Case 2: A 28-year old scientific collaborator of the mycologist became sick at about the same time with febrile mylagin in the region of the right thoracic musculature. The chest X-ray by a lung specialist on February 1, 1964 gave an atypical pneumonia in the right middle field which was at first taken to be tuberculosis and led to hospitalization.

On admittance on February 2, 1964 there was fever of 38.2° auxillary, tachycardia of 90/min, irritative cough with expectoration of a whitish foamy sputum, urticarial exanthema on the trunk, which was interpreted as the result of an unrelated chloramphenicol (chloromycetin) treatment. Bronchovesicular respiration was found by auscultation especially over the right middle-upper field. The blood picture showed leucocytosis of 10,400 with displacement to the left corresponding to 7% rod nuclei, 75% segment nuclei, 2% eosinophils, 15% lymphocytes, 1% monocytes, sedimentation speed at 43/77 mm. Our first X-ray picture of the chest of February 2, 1964 indicated not sharply delimited infiltration in the lateral segment of the right middle field as well as a less intense, likewise not sharply delimited shading in the right lower field and left pericardially with enlargement of the hilus glands bilaterally (Figure 3).

The patient assisted in the aforementioned differentiation experiment of the hyphomycetis culture on January 2, 1964, therefore an infection with coccidioides immites could likewise be assumed.

Tubercle bacteria were never found in the sputum, however, on February 22, 1964, fungi of the type coccidioides immites were demonstrated microscopically and culturally (Institute for Hygiene and Microbiology of the University of Wurzburg, Director: Professor Dr. C. Sonnenschein).

The intracutaneous coccidioidin-test on February 26, 1964 gave a three-fold positive, the complement binding reaction gave a titer of 1:8 coccidioidomycocis (Walter Reed Army Medical Center).

This patient showed a relatively bland disease course with good general condition and prompt recovery from fever on the third day of treatment. The blood picture on February 21 showed a transient eosinophilia to a 17% maximum. An erythema-nodosum similar to exanthema occurred on March 1 on the hands and armpits which disappeared again after four days

without further therapy. The complement fixation test remained constant in further checks. The pulmonary infiltrates progressively regressed by themselves with intermittent hilus swelling bilaterally under symptomatic therapy within six weeks with normalization of the blood picture and blood corpuscle sedimentation rate. Our final chest X-ray examination on March 9, gave a cherry-sized thin-walled cavity in the right middle field. In a checkup on December 21 no more fungi were demonstrable in the sputum. The chest X-ray checkups still showed a cherry-sized residual shadow in the right middle field, a cavity was no longer demonstrable (Figure 4).

Discussion

Cause, Occurrence and Course

Coccidioidomycocis, also known as Valley- or San Joaquin fever, is a mycosis produced by the fungus coccidioides immites in the southwestern U.S.A.[8,38] The morbidity amounts to more than 35,000 cases per year; the morbidity among the local population fluctuates between 8 - 25% yearly.[31] The endemic occurrence is observed in southern California, southern Nevada, Arizona, west Texas and New Mexico, disease cases also having been reported in South America and Italy.[16,19,34]

Transmission occurs through dust contact with the fungus spread chiefly by sheep, dogs and rodents.[5] The literature especially refers to the frequency of a laboratory infection through working with dry culture material.[15]

The primary infection results, aside from isolated cases of a primary cutaneous coccidioidomycocis,[11,12,13,36,37] as a rule, through dust inhalation of cellular sporangia,[24] which multiply in the organism through endosporulation growing on artificial nutrient media forming hyphae and mycelia.[1]

The primary pulmonary disease form is benign, in many cases runs sub-clinically and is then only demonstrable by a positive skin test to intradermal injection of Coccidioides.[30] Frequently, however, an influenza-type disease exists with exhaustion, slight fever, weight loss, chest pain and a mucous, purulent, partially blood-stained sputum. In one-third of the cases lung infiltrations of confluent or nodular types with hilus enlargement occur in the primary stage and cavities can already develop early on.[3,39,41] In 3% of the cases, several days after the waning of the febrile period there occur allergic symptoms in the form of an erythemanodosum or erythema multiformans, whose benign erythemateous nodules are often indistinguishable from a disseminated coccidioidal skin

granulomas.[14]

Dissemination occurs by endogenous reinfection[25] which usually manifests itself shortly after the primary infection; occasionally, however, it is only obvious after several years and can affect all organs except the gastro-intestinal tract.[9]

The progressive granulomatous form appears clinically as intermittent fever, persistent cough, marked weight loss and continuous abnormal pulmonary changes in increasing complement fixation titer.[4] In 0.2% of the cases in the latter stages there develop the dreaded coccidioidomycoma, which can, in turn, fuse through cavity formation and show a progressive course spreading in skin, bone and meninges.[1] Regional lymphadenites and osteitis can lead to chronic fistular abscesses on the [German can mean any of these four: neck, throat, cervix, isthmus], mediastium and extremities. Metastatic abscesses have been described in liver, spleen, kidneys and adrenals, gonads and brain. The pulmonary consolidification can lead to abscess formation and empyema, a myocarditis or pericarditis and an acute or chronic meningitis can develop.[33]

Diagnosis and Therapy

The intracutaneous coccidioidin reaction (coccidioidin 1:100, Cutter Laboratories) was used for diagnosis, wherein occasionally cross reaction with histoplasmins and vice versa occur.[7,23,26,27,28] For positive skin reactions the serologic complement binding reaction should be carried out, which is suspected at a titer of 1:8, if a still higher titer of histoplasmosis is not found simultaneously. Serially increasing titers conclusively indicate progression of the disease.[29]

The diagnosis is confirmed by the microscopic demonstration of the germ in sputum, better yet by cultural demonstration of the germ in Sabouraud's agar or beerwort-nutrient medium and most reliably by innoculation experiments in mice or guinea pigs.[10]

The treatment of primary pulmonary coccidioidomycocis is purely symptomatic, even when cavity formation has set in. It extends first of all to careful and repeated X-ray and serologic surveyance of the patient. If isolated cavities remain longer than six months their resection should be commenced.[17,21] Resection is advised especially in recurring hemoptysis (60% of patients), cavities of more than 2 cm

diameter, subpleural localization with danger of a rupture in the pleural cavity (2% of patients with cavity remnants), as well as in secondary infections with anti-bacterial therapy resistance.[20,40] If solitary remnant foci, i.e., cavities and coccidioidomycomas, are demonstrable then the X-ray and serologic surveyance of the patient should be extended over two years. The local spreading of an abscessing coccidioidomycoma, the peripheral extension and transpleural rupture of cavities as well as the onset of recurring cavities and post-operative bronchopleural fistulae[6,23,35] can be kept under control with definite surgical and antibiotic treatment.

For drug treatment of progressive granulomatous coccidioidomycocis Amphotericin-B is suggested, Winn[42] recommends Amphotericin-B-therapy:

1. In persistent fever, elevated blood corpuscle sedimentation rate with severe pulmonary complications and hilus adenophathy,

2. In instable serology, i.e., increase in complement fixation titer above 1:64, persistent precipitation, incomplete complement fixation,

3. In disseminated pulmonary foci, i.e., coccidioides immites invasion of other organs,

4. In weak or negative skin reaction to coccidioidin,

5. In relatively dark skinned races,

6. As antibiotic protection in surgical intervention, thus in pulmonary cavity resection or damaged lung region, removal of infected bones, gonads, lymph nodes, abscesses and sinus tracts. Further, in combination with high-frequency coagulation of granulomatous skin lesions and super-infected abscesses.

7. In certain situations of metabolism as pregnancy and diabetes mellitus.

Prognosis

The prognosis of primary pulmonary coccidioidomycocis is always good considering its tendency for spontaneous cure. In the majority of cases the infection goes away after passing through the benign primary stages and leaves lifelong

immunity. Only in 5% of cases there remain pulmonary residua such as cavities, solitary coccidioidomycomas, fibrous scar regions, localized bronchiectases, and calcified hilar nodes. The pulmonary remnant cavity closes [illegible] spontaneously in 35% of cases, coccidioidomycoma only rudimentarily. In less than 0.5% of cases deficient [illegible] of the primary infection leads to organ dissemination. The course of the progressive granulomatous form in the long view always has an unfavorable prognosis; its mortality amounts to 60%, even when intervening remissions occur. The coccidioidal meningites usually ends in death.

Transfer from man to man has never been observed, accordingly, there is no basis for isolating patients.

Differential Diagnosis

For differential diagnostic purposes it is necessary to consider other pneumomycoses in their acute and disseminated stages, such as the septically progressing Candida- or Aspergillus-infection of the lungs which was described previously by Wollheim and Braun[44] in the German literature.

First of all, in the various parts of North, Central and South America the partly endemically occurring histoplasmosis and blastomycosis must be considered.

Finally a progressive cryptococcous infection of the lungs, an actinomycosis and its closely related nocardiosis as well as the rare sporotrichosis- or mucormycosis-disease of the lungs must also be mentioned.

Further parallels are obvious roentgenologically with the various forms of tuberculosis.[43] Thus a tuberculosis early infiltration resembles the primary pneumonia of coccidioidomycocis. The latter progresses, however, more benignly even when small primary cavities occur, for which our second patient serves as an impressive example. In both diseases a pleural effusion or an empyema can occur, which in coccidioidomycocis in 2% of cases follows transpleural rupture of a peripherally located residual cavity.

Multiple pulmonary infiltrations can simulate an extended tuberculosis as well as a metastatic lung disease.

An isolated coccidioidomycoma can resemble a peripheral bronchogenic carcinoma. The solitary pulmonary residual focus, however, tends to abscess and is usually surrounded by nearby granulomatous satellites.

Thin-walled pulmonary residual cavities are in coccidioidal disease eventually surrounded by infiltrations, which persist as remnants of the primary pneumonia and are not usually caused by bronchogenic reinfection from the cavity itself. This picture must be differentiated from bronchiol pneumonia by grafted virus- or bacteria-secondary infection.

Military pulmonary lesions of a disseminated coccidioidomycocis cannot be conclusively distinguished from a military tuberculosis.

Summary

In two cases, as a result of a laboratory infection, pulmonary coccidioidomycocis occurred. The diagnosis was confirmed by intracutaneous coccidioidin -reaction and by the complement fixation test as well as by microscopic and cultural demonstration of the germ. The course of the illness was in both cases relatively mild, the pulmonary infiltrations receded under nonspecific therapy within several weeks. In progressive granulomatous coccidioidomycocis treatment with Amphotericin-B should be considered.

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