Family Practice Grand Rounds

Primary Tuberculosis in a 25-year-old Man

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DR. WILLIAM VONDERHAAR (*Chairman, Department of Family Practice*): Today's Family Practice Grand Rounds will address the subject of primary tuberculosis in a 25-year-old man, together with related questions concerning the care of his family. Various aspects of diagnosis and management will be discussed. Following presentation of the case, we will call upon Chest and Radiology consultants to expand on specific issues. We are also fortunate in having with us today a guest, Dr. Jerry Smith, who has been in Rhodesia before returning to Louisville.

JAMES REDMON (*senior medical student*): Our patient today is a 25-year-old Caucasian man who presented to the St. Anthony Hospital Emergency Room on Tuesday, December 3, 1974, with the chief complaint, "I've been coughing up blood." He first noticed he was ill on Friday, November 29, 1974, when he began experiencing sharp chest pains localized to his left upper chest. He stated that the pains intensified upon deep inspiration. He also had a headache during this period, and he was feeling run down and felt that he might be getting the "flu." He left work that Friday, went home to bed and took self-medication consisting of "Contac, four-way cold capsules and cough syrup." On Saturday his temperature was 102 degrees. He stated that he had night sweats only once, on Monday night, and he denied chills. Although he was eating well, his food "had no taste to it." He stated that he had been losing weight, approximately 24 lbs in two weeks. On Tuesday morning he went back to work, but felt worse than on Friday and, therefore, returned home. On the night of December third, he was sitting quietly on the sofa eating ice cream and watching television, when he began coughing. This soon produced gross blood and lasted approximately 20 minutes. He stated that he coughed up about "one pint of almost pure blood." The family took him to St. Anthony's Emergency Room, where he again began having gross hemoptysis and was admitted.

The patient's father had tuberculosis three to five years ago and was treated at Hazelwood Sanatorium for approximately one week. The patient had one uncle who died with tuberculosis. Moreover, a second uncle and an aunt both presently have tuberculosis. The patient had a tine test and chest film in 1971, both of which were negative. There is no other known history of exposure to tuberculosis.

The patient is employed by a local subcontracting firm as a machine operator, and his particular job is burying telephone cables. This requires his spending the entire working day out-of-doors. He has not been outside of Louisville in the last 15 years. He once was a very heavy drinker, but he denies any ethanol intake in the last six months. He admits to smoking ten to 12 packs of cigarettes a year.

The patient denied a past history of hemoptysis, orthopnea, paroxysmal nocturnal dyspnea, pneumonia, or bronchitis. He stated that he has recently had more shortness of breath than he had several years ago, a fact which he attributes to his smoking. He denied significant sputum production. The remainder of the review of systems and past history was essentially negative.

On physical examination the patient's height was 5 ft 10½ in., weight 124½ lbs, respirations 20, temperature 104 F, pulse 98, and blood pressure 114/54. He appeared his stated age of 25 and had good muscle mass despite decreased panniculus; he showed no apparent muscle wastage over the shoulder girdle. He was experiencing some acute distress and he frequently coughed up a current jelly-like sputum. He was alert, oriented, and cooperative.

Examination revealed slight decrease in expansion of the left upper chest. There was some decrease in breath sounds posteriorly under the

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left upper lobe, and Krönig's isthmus appeared slightly narrowed on the left side. The lung fields were clear to auscultation, and no amphoric breathing, crackpot sound or post-tussive rales were noted. Breath sounds were bronchovesicular with suggestion of bronchial breathing anteriorly over the left upper lobe. No cyanosis or clubbing was noted and the rest of the physical examination was essentially normal.

DR. T. P. WILDER (*third-year family practice resident*): The patient was placed in a private room with precautions to guard against inhalation of contaminated droplets. He continued to complain of severe left side chest pains, and he exhibited a low-grade fever with erratic temperatures recorded at 102 F to 103 F. He continued to raise copious amounts of bloody sputum. Laboratory studies showed a hemoglobin of 12.5 gm percent and his hemogram was otherwise normal. Urinalysis and multichanneled chemistry tests were normal. An intermediate strength P.P.D. was applied on admission. At 48 hours there were 20 mm of induration. Histoplasmin skin test was negative. Complement fixation tests for fungi were also negative. Sputum specimens were obtained daily for acid-fast bacilli, as were sputum cultures for fungal organisms. Bacterial cultures were nonremarkable. After three sputum smears were shown to be positive for acid-fast bacilli, triple drug therapy was instituted for tuberculosis on the third hospital day. The drugs used were isoniazid 300 mgm, ethambutol 800 mgm, and rifampin 600 mgm, every morning. The patient was followed closely for adverse drug reactions, especially those affecting vision. The patient's fever showed a gradual descent until he was afebrile on the seventh hospital day. His chest pains subsided and the production of bloody sputum diminished markedly. His appetite returned and the patient felt generally much improved. He was given generous meals and gained approximately 6 lbs in the course of two weeks.

Sputum examination on the tenth hospital day showed numerous acid-fast bacilli on the concentrated smear. No significant side-effects of the drug therapy had been noted. The Public Health Department was contacted. Its investigations showed that the patient's wife had a positive P.P.D. and a normal chest x-ray. INH prophylaxis was recommended. The patient's only child had a negative skin test, but the patient's sister exhibited a positive skin test and was placed on INH.

DR. J. WHALEN (*Chief of Radiology, St. Anthony Hospital*): A series of three chest x-rays were taken of the patient. (See Figures 1 and 2) On the initial films (December 3, 1974) there is an infiltrate in the posterior segment of the left upper lobe in the apical region. On the lateral view this involves primarily the posterior segment of the left upper lobe. There is also some alveolar infiltrate. There is possibly some involvement of the superior segment of the lingula. The lesion of the left upper lobe has a large cavity in it. There is a fair amount of reaction around it with consolidation.

The progress films show that extra therapy is indicated. The cavity is smaller, both on December 11 and December 20. By December 20, the area of infiltrate around the cavity has reduced in size by almost half. The last x-ray shows involvement of the inferior segment of the lingula. You will note that the patient loses the heart borders and the silhouette sign, indicating that he has involvement of the lingula on the left side anteriorly. This has the appearance of a fluffy infiltrate. This is a complement bronchial spread and is not a typical miliary spread. The right lung remains clear, in spite of the spread on the left side. He does have evidence on the chest films of minute calcifications from old disease in the past, and you can also notice up by the axilla that he has a calcified lymph node. In old tuberculosis, calcified lymph nodes occur primarily in cervical areas and secondarily in the axillary region. Tomograms taken of this patient demonstrated the consolidation in greater detail, revealing the cavity to be smooth in outline, as distinguished from the cavity with ragged outline which would be present in the case of abscess or tumor.

DR. WILLIAM ANDERSON (*Chief, Pulmonary Diseases, University of Louisville*): We have three problems to consider here: the patient, his two adult contacts who have positive skin tests, and his infant child who is still skin test negative.

First, to consider the patient, it is interesting that Dr. Whalen has pointed out evidence of probably preexisting tuberculosis in spite of the fact that this patient was said to have had a negative skin test and x-ray in 1971. We would expect, or at least we are not surprised, that he would have evidence of old tuberculosis. He has what we consider a "bad" family history. This is the sort of family that gives rise to the expression in the laity of "tuberculosis running in families," and there are many people who consider tuberculosis hereditary. It may be that this family is less resistant to tuberculosis than many other families, and there has been close contact within the family unit in the past. The Public Health Service has found in various studies that about 80 percent of adults who have tuberculosis represent endogenous reinfection – an exacerbation of old, previously-healed tuberculosis – and this would go along with the changes that Dr. Whalen has pointed out and with the patient's family history.

The diagnosis was easy in this instance, since the sputum was readily positive. In a man who works out-of-doors as this patient does, and especially in the Ohio River Valley, we have to think about the possibility of fungus, as you did. We have almost given up doing skin tests for histoplasmosis because this does not really contribute anything and occasionally creates confusion by causing changes in the complement fixation, which should certainly be done.

Once the diagnosis is established, we are then faced with the problem of treatment. In my opinion, this patient is receiving the proper treatment. One drug will rarely be adequate in someone who has far advanced tuberculosis, as this man does with evidence of endobronchial spread to the adjacent lobes. INH is an excellent drug, but if INH is given alone in instances like this, we have an extremely high rate of development of drug resistant organisms. If a second drug is given, we can markedly reduce the emergence of resistant organisms. Para-aminosalicylic acid (PAS) has previously been considered the drug of choice to prevent the emergence of resistant organisms. Unfortunately, PAS often has a high rate of patient unacceptability. A number of studies have shown that up to 40 or 45 percent of patients do not take PAS, or take less than the prescribed dosage, because of disagreeable gastro-

intestinal side effects.[1] Ethambutal has now come forward as the drug to primarily replace PAS. Ethambutal, in combination with INH, is no better than PAS in preventing the emergence of resistant organisms, but it has far less toxicity and is much more acceptable to the patient. We must be concerned with eye toxicity when using ethambutal, but this is very low if we do not exceed the dosage of 15 mgm/kilo. I personally have not seen a case of ophthalmic toxicity where the drug had to be stopped when it was given in this dose. However, I feel we are obliged to check both the color vision and the visual acuity of patients before we start them on treatment. If we detect an abnormality before treatment, we can then know, if the patient starts complaining later on, that it is not ascribable to the drug.

We must consider whether two drugs are enough in a case like this. In the past, most of our information regarding tuberculosis came from the VA-Armed Forces Cooperative Studies which were carried out over a period of some 27 years. These studies were discontinued about three years ago since the number of cases of tuberculosis had dropped off markedly, and good regimens of drug therapy had become quite standardized. A study in the early 1960's looked at the use of two drugs versus three drugs in patients with advanced tuberculosis. The drugs at the time were INH and PAS, and the three-drug combination added streptomycin to these two. At the end of six months, it was found that the number of individuals with negative sputum and the number of individuals with closure of cavity were identical in the two groups; the only significant difference was that the group which received three drugs had more drug toxicity.[2] At the end of two years, however, it was found that the number of people who had relapsed, or who still had persistently positive sputum, was exactly twice as great in the group receiving two drugs as in the group receiving three drugs.[3] Since this information became available in 1968, most of us who have been involved with treatment of tuberculosis in individuals with far advanced disease, especially when it involves more than one lobe, such as in this patient, have felt more confident of the long-term results if we give three drugs rather than two. In this case, the patient should have twice as good a chance of being well and of having negative sputum at the end of two years by starting on three drugs instead of two.

Our next question is how long should the patient receive three drugs? We generally treat tuberculosis in segments of about six months, so this patient should receive these three drugs for six months. At that time we should reevaluate him for conversion of sputum to negative, closure of his cavity, return to normal weight, and disappearance of sputum production. If all these things have happened, we can then stop one of the three drugs. In that instance, rifampin should be discontinued since it is the most expensive of the three. The patient would then be continued on the two drugs and we would reevaluate him again six months later, at the end of a year of treatment. If everything is going well at that time, we continue the other two drugs with the expectation of finally completing an additional year's worth of therapy.

Recent evidence has suggested that there may be at least an additive effect as far as hepatic toxicity is concerned between INH and rifampin, particularly in alcoholics. Despite the possibility of some hepatic toxicity, however, we use these drugs on the basis of recent evidence from both animal and human studies that this combination of drugs is truly bacteriocidal for tuberculosis, not merely bacterioastitic.[4,5]

Let us now consider the patient's wife and sister. The degree of positivity of their skin tests greatly influences how we deal with them. If the intermediate skin test is positive to the extent of 20 mm or more, treatment is imperative. If their chest x-rays are negative, present opinion holds that INH is sufficient treatment. If their skin test is positive to the extent of 20 mm or more, they have roughly 17 times the probability of developing tuberculosis in the next five years as compared to someone with a skin test of less than 10 mm induration. To put it another way, they have a chance of about one in 30 of developing tuberculosis.[6] These chances are great enough to warrant the expense, which is not great, of giving INH and of accepting a relatively low order of toxicity. If their skin test is 10 mm or less, this is essentially negative and we would not treat them. The difference of opinion arises in the case of adults with positive skin tests between 10 and 20 mm. Some would prefer to watch such individuals by repeating x-rays at three-month intervals; if their x-rays stay negative, they are not treated. There are others who feel that they should be treated. I believe that individuals who have converted their skin test (above 10 mm) within the last year should be treated with INH. INH does not prevent all tuberculosis, but it cuts it down by a factor between three and four.

Turning next to the ten-month-old baby, we must carefully consider the question of drug therapy. I recall seeing several infants, exposed to tuberculosis and with negative skin tests and chest x-rays, whose first manifestation of illness was tuberculous meningitis. My own feeling would be to suggest that this child be placed on INH in the appropriate dose for his weight, but you may also want to seek pediatric consultation on this point.

Further Case Discussion

DR. BARRY BRUMBERG (*third-year family practice resident*): What about the use of BCG?

DR. ANDERSON: In the case of this family unit, the only one we would consider for BCG would be the child. It takes some time for BCG to be effective. BCG's protective effect lasts for between five and seven years. Comparative studies have shown that INH is somewhat more effective than BCG in preventing tuberculosis in the individual patient. In the case, however, of a group of people who have a relatively high probability of developing tuberculosis, such as Alaskan Eskimos, there may be some merit to giving BCG rather than INH. BCG need be given usually one time only, while INH has to be taken every day. In addition, there is considerably less cost involved in giving BCG to a large group of people, compared to the cost of INH for a year at a time. I believe there is a place for BCG in some Public Health Service situations, but I'm not sure that any exist in this country at this time, although in other parts of the world they most certainly do.

DR. DONALD DIEBOLD (*Department of Family Practice faculty*): In this case of a patient who has such a

large cavity, would surgical intervention be indicated or would this probably heal with the treatment that he is getting?

DR. ANDERSON: The chances of this cavity healing are about 95 out of 100, and even if he is left with a cavity, it still does not necessarily mean that surgery would be required. Over the last five to six years, surgical intervention in tuberculosis has nearly been abandoned. If this patient still has a cavity at the end of a year, he can be considered to have an open-healed tuberculosis. There are some individuals who retain persistent cavities for an indefinite period of time because of endothelium from the bronchus growing in and lining the cavity. Surgery does not really have much to offer in the treatment of tuberculosis nowadays. We still see patients who were treated surgically in earlier years, and we have been disappointed at the high rate of development of cor pulmonale in these patients. Of course, back at the time when surgery was performed they might well have succumbed to their tuberculosis had such procedures not been instituted.

DR. PAUL GRIDER (*internist, Department of Family Practice*): How would you approach this patient diagnostically if you obtained negative sputums?

DR. ANDERSON: If the sputums that he is producing are negative, we use supersaturated mist to induce sputum. If four induced sputums are still negative for tuberculosis, we proceed with fiberoptic bronchoscopy and aspirate material directly from the cavity. In this way, we can expect, in most instances, to make a definitive diagnosis of tuberculosis, carcinoma or fungus.

We should also discuss other aspects of this case, such as the duration of hospitalization, the extent of contagious precautions, and the duration of disability.

Previously, patients with active tuberculosis were often treated from one to two years in a sanitorium. As you all know, our sanitoria are mostly closed down today. This is due mainly to recent changes in the treatment of tuberculosis rather than to the decrease in the number of cases, although the number of cases has decreased markedly.

We have evidence that after a patient such as this man receives between two and three weeks of antituberculous treatment, he is relatively noninfectious.[7] His organisms are sick organisms after they have been bombarded with these three very effective drugs. While you still may be able to secure acid-fast bacilli in the sputum, if you inject that sputum into guinea pigs they will not become infected. Such acid-fast bacilli have lost their virulence and their ability to infect people. It is usually perfectly all right to let cooperative individuals leave the hospital at the end of about three or four weeks, and to shift their treatment program from the hospital to the home, with periodic visits to the clinic. We tell such patients to avoid close contact with their children for a while.

The question of return to work is another important matter which we must consider. Although he may be getting along fairly well and have nonvirulent acid-fast bacilli after the first three to four weeks of treatment, the patient would not do well if he went back to work and acquired a bacterial pneumonia. I would therefore prefer to see this man stay off work until the severe winter weather is over and the chances of his acquiring a bacterial pneumonia from outside exposure are minimized. Along in March or April there should be no contraindication to his returning to work, assuming he has continued to take the medication and is getting on as well as we expect. He would be of no danger to his fellow workers by that time. The old axiom that you do not get tuberculosis from people under treatment is still a very valid one.

DR. GRIDER: Haven't we seen an unusually rapid resolution of the cavity in this patient?

DR. ANDERSON: The resolution is of the infiltrate surrounding the cavity. If we did laminograms right now, the patient would still have his cavity. On the first film he has what we would call a tension cavity without open communication with the bronchus. It is likely that this cavity subsequently emptied out infectious material which was aspirated into the lower portion of the lung.

DR. WILDER: If he does not take his drugs regularly and develops a recurrence of active tuberculosis, what would you do then?

DR. ANDERSON: If he does not take his drugs regularly, he will develop drug-resistant organisms. The usual situation is that such patients return in four to six months with hemoptysis. Hemoptysis always motivates patients to be more concerned with their illness. In that event, you would expect to find that this patient would have worse disease in both his left upper and left lower lung, and he might even have spread over to the right side. In patients with drug-resistant disease, INH plus two drugs they have never received before should be given to them. Fortunately, INH-resistant organisms are relatively avirulent. A patient who has become resistant to INH, ethambutol and rifampin would probably be started on another regimen such as INH, perizenimide, and cyclocerene.

DR. VONDERHAAR: Dr. Smith, do you have any comments about tuberculosis in Africa, since you have been over there for the last three years?

DR. JERRY SMITH (*Department of Family Practice faculty, Louisville Memorial Hospital*): This is very typical of the type of case that we see. Tuberculosis is very common, including miliary tuberculosis and tuberculous meningitis. I would reemphasize what has been said about BCG versus INH in economically developing countries. In our larger African hospitals, we have five million Africans versus some two hundred thousand whites; we routinely give the BCG to all the African babies that are born in the larger hospitals. In addition, we are still using streptomycin, INH, and PAS because of the cost.

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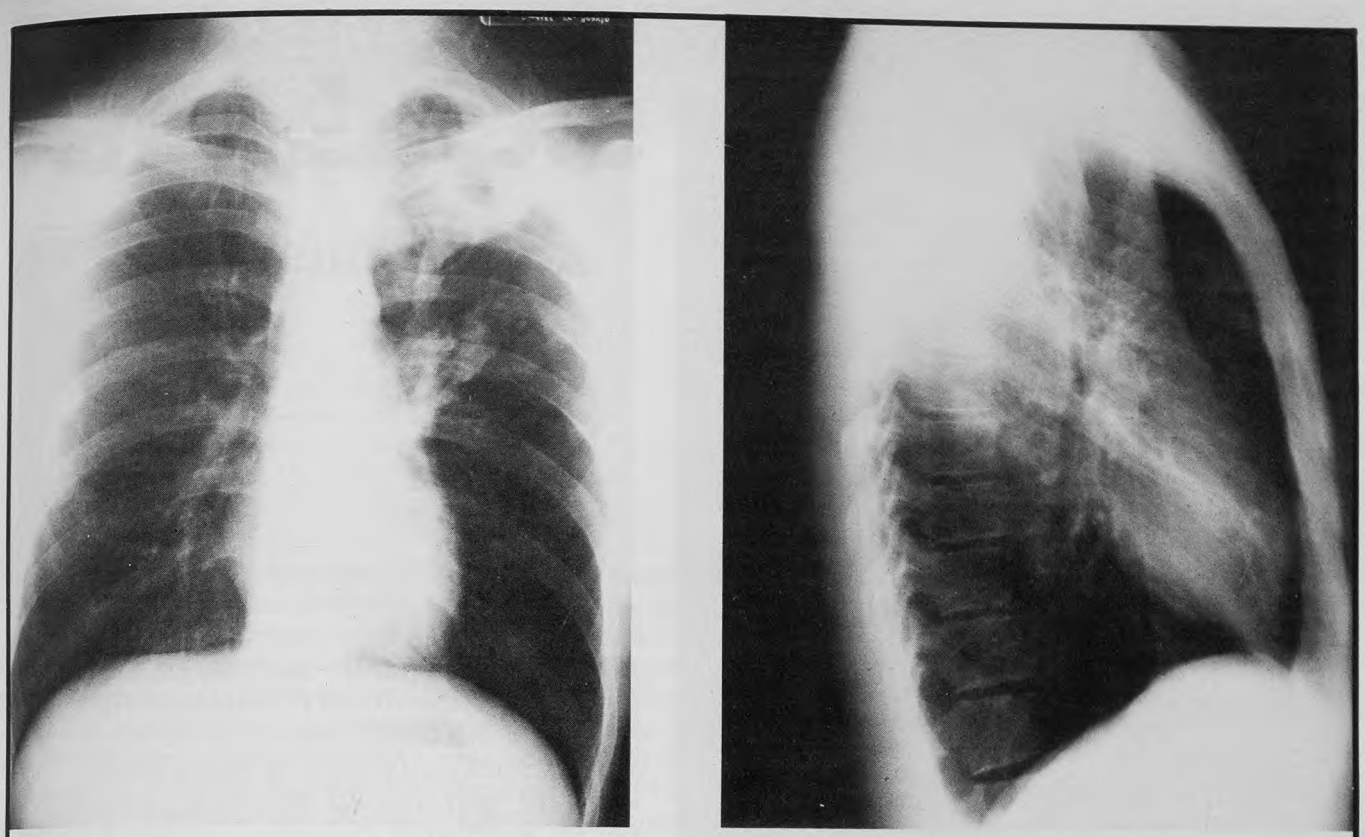

Figure 1. *Left:* Chest film on December 3, 1974, showing infiltrate and cavity formation in the left upper lobe in the apical region. *Right:* Lateral view showing infiltrate involving primarily the posterior segment of the left upper lobe

Figure 2. *Left* (AP view) and *Right* (Lateral View): Followup chest film on December 10, 1974, showing reduction in size of infiltrate around the cavity and involvement of the lingula on the left side anteriorly