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MODERATOR: —to begin this afternoon's Grand Rounds. We're going to do something this afternoon that is often not done at Grand Rounds anymore, and that is, we're going to discuss patients, and how we diagnosis and treat them. We have chosen two unusual patients that were on the medical wards. The first patient will be presented by Dr. [Richard C.] Hubbard. [Pause]

HUBBARD: The patient was a 42 year old white man with a history of hairy cell leukemia, who was admitted to the hospital because of recurrent febrile illness. He was in good health originally, until four years prior to admission, when a diagnosis of hairy cell leukemia was made. At that time, a splenectomy was done. The patient was clinically well thereafter, until four months prior to admission, when a febrile illness developed following a trip to Acapulco, Mexico. He was given erythromycin for therapy of a respiratory infection. He then developed fevers to 104 degrees, with night sweats.

A chest film taken then showed a new—it should be right lower lobe infiltrate, this is slide number one. [pauses] Okay, it shows a right lower lobe infiltrate, as well some increased lung markings in the right upper lobe area. A bronchoscopy was done at this time, including a lung biopsy, which just showed a round cell infiltrate consistent with leukemia. A PPD was negative, with positive controls, as were AFB smears. A ten-day course of erythromycin, tobramycin and cefamandole was tried, with defervescence only after completion of the antibiotics.

The patient left the hospital, and was soon readmitted for recurrent fever, and underwent a mediastinoscopy which revealed non-caseating granulomas. He was discharged with a diagnosis of presumptive tuberculosis, on a therapy of INH and rifampin in full doses, and 30 milligrams of prednisone daily. At home, fevers recurred, and ethambutol was added. AFB cultures of mediastinal nodes from the mediastinoscopy were negative after six weeks. The patient was readmitted early in July of 1981 for recurrent fevers, while being treated with INH, rifampmin and ethambutol. His past medical history was notable for hairy cell leukemia as mentioned, and he had chronic leukopenia and thrombocytopenia. Following his trip to Acapulco, he had what he called Montezuma's revenge, a brief diarrheal illness. His medications are those listed, and the only other history of note is that he had a cat at home. His occupational exposures were negative.

His physical examination: when admitted in July, he had a temperature of 102 degrees orally. His pulse was 110; blood pressure 110 over 60. The pertinent findings were a pale—were pale skin without ichorous, petechiae, or skin rash. He had clear lungs, a grade one over six systolic murmur with crisp, normal valve sounds. The liver was slightly enlarged by percussion, without a palpable edge. A well-healed midline laparotomy scar from his splenectomy was

present. There was no regional adenopathy. Trace pedal edema, with a normal neurological examination.

The laboratory results are as noted on the protocol sheet. Of note, there was pancytopenia, a slightly elevated alkaline phosphatase. A chest x-ray, this next slide please. Next slide. Do I have the—? It shows clearly of the infiltrate that was previously present. During the hospitalization, empiric therapy with cephamandole and tobramycin was begun. Anti-tubercular drugs were stopped. Because of persistent fevers and the growth of an organism from a liver biopsy, therapy was changed to vancomycin and gentamycin.

During his hospitalization, the following test results were obtained. He had multiple negative blood cultures because of persistent fevers. At least ten of them were done; they were all sterile. Multiple urine cultures were also negative. Stools for ova and parasite were negative, as were malaria thick smears. Febrile agglutinin, toxoplasma, CMV, herpes virus, Coxsackie titers were all done and were all negative. Urinary and gastric aspirates for AFB were negative. Legionnaires, histoplasma complement fixation, aspergillus complement fixation, and Q fever titers were all less than one to four. Liver biopsy was done. The culture of it grew only Strep viridans. There were no granulomatas seen on the liver biopsy. Finally, an abdominal CT scan was done, which showed large para-aortic lymph nodes. Because of persistent fevers, a final diagnostic procedure was done, which was a blind axillary lymph node biopsy. [Pause]

MODERATOR: Well, I don't know whether this was evident to all of you, but really, in order to make the diagnosis in this case, the physicians really had to be persistent. And the fact that an invasive procedure was done once, and was actually—and did not yield a diagnosis -- did not preclude repeating such an invasive procedure in the face of the clinical findings that really demanded that it be repeated. The patient, of course, didn't want this done again, but the biopsies were done—were finally repeated, and this time they did yield a diagnosis of *Histoplasmic capsulatum i*nfection, and Dr. [Ed] Bottone will tell us a bit about the microbiology and the culture of this organism. I should also say that it is very important for the clinician to really check all the materials that are taken from his patient, because the diagnosis was missed on the original slides.

BOTTONE: As you may well realize, whenever a diagnosis of histoplasmosis is made, it's attended by a great deal of excitement. But most of these diagnoses are made not in terms of a direct marked biological approach, because the organism is rather difficult to grow. And unless there is a suspicion for its presence, and we're not alert in the laboratory, frequently, specimens may be discarded as—the culture made discarded long before the organism has a chance to grow. It requires at least up to a month incubation and constant surveillance to recover this microorganism.

In this particular case, as you'll see in the first slide, it was really by a cooperative effort, actually, with the Pathology Department. The diagnosis of histoplasmosis was made initially by

seeing the organisms in the biopsy of the lymph node that was performed. This is at the very end of this patient's course. And the diagnosis [was] made by visualizing these sort of round, ovoid organisms, somewhat indistinct - in an H and E stain as shown here - nevertheless, somewhat characteristic. They seem to be surrounded by a clear area, which is really somewhat of an artifact. The name *Histoplasmic capsulatum* does not denote that the—the fact that the organism has a capsule, because it does not. This is the staining artifact; that's re-shrinkage.

And when Dr. Darling [Samuel Taylor Darling in 1906] originally described this, looking for Donovan bodies, he thought that indeed, these were capsules. When they are associated with a histiocyte or a macrophage, a diagnosis can be somewhat easy. And sometimes they lie free, and they're a little bit indistinct by the H and E preparation. At the time these were visualized on H and E, Dr. Ira Schwartz from the Pathology Department called us in the Microbiology laboratory. The cultures that we had, the plates had already been discarded, but we still had part of the lymph node specimen in a tube of broth medium.

After his phone call, we re-cultured the lymph node specimen, and indeed, as I'll show you, were able to recover *Histoplasmic capsulatum*. In the absence of, let's say, clearly distinguishing the microorganism in H and E stains, methenamine silver stains, as shown here—this is from an old granulomatous lesion—will frequently reveal the presence of the organism, as shown here, as a budding yeast-like organism. And that is the only morphologic criteria that one has to identify this particular microorganism.

However, the cultures become important, because histologically, this form is not terribly different from, let's say, that which might be presented in tissue by *Torulopsis glabrata*, and we have seen an instance here where a diagnosis of histoplasmosis was made, histologically, in a patient who had had *Torulopsis glabrata fungemia*. And indeed, when we did some additional studies, it turned out that the organism was indeed Torulopsis and not Histoplasma. So there is a question, and a definitive diagnosis then comes from cultivating the microorganism. As I mentioned, following Dr. Ira Schwartz's call to the laboratory, we began to proceed with the diagnosis.

Another diagnostic approach directly can be from bone marrow aspirates, which would show the typical budding yeast-like organism as you see it here. Again this is a Giemsa stain smear which shows these budding forms, or these round ovoid forms, quite clearly. We do not often see it as nicely as it is demonstrated in this particular slide. Culturally, after Dr. Schwartz's call, we plated and re-plated the specimen, and held it for a prolonged period of time, and finally we got a few colonies to grow. And on subculture, these grew a lot nicer, as you can see it here, and began to fill the tube up.

This is a dimorphic fungus. That is, at 30 degrees and above, it'll grow as a yeast-like organism, and below 22 degrees it will grow as a fungal form. The diagnostic structures that we seek in the laboratory are really present in this mold-like fungal form, as you see it here. When we tease some of this growth apart, what one looks for in this phase-conscious photomicrograph, are these round, ovoid, sort of—these are called microconidia, shown here, and the characteristic structure, the diagnostic structure is this round, so-called tuberculate

macroconidium, or macro-aleuriospore, as shown here, and better defined in this particular photomicrograph. Again, this is the diagnostic structure, the so-called tuberculate macroconidium that characterizes Histoplasma capsulatum. And it is on that basis, with the combined pathology findings and the cultural characteristics, that Histoplasma capsulatum was diagnosed. [Pause]

MODERATOR: I should also say that when one does have a very difficult case, and you have tissue that was obtained at the patient's expense, a call to Dr. Bottone, who's Chairman of the [Mount Sinai Hospital] Department of Microbiology, would be worthwhile, and he would appreciate it, because that way, you can see that the tissue is properly handled.

Well, we are fortunate today to have Dr. [Jack] Rabinowitz with us, who's Chairman of the Radiology Department. And we happened to note, on our way to see x-rays, that they have a lovely exhibit on the radiology—the radiographic findings in histoplasmosis. And I thought that it would be very fitting for Dr. Rabinowitz to share this with us this afternoon. [Pause]

RABINOWITZ: I think one of the main things to stress is the fact that sometimes radiographic findings of histoplasmosis and tuberculosis are practically almost look-alikes. In fact, they behave very similarly, they give very similar type of radiographic pictures, and the only difference is that there may be a difference in severity and extent, and in certain specific manifestations which help you—allow you, at least, to make a certain diagnosis, or differentiate histoplasmosis from tuberculosis. The main reason, of course, would be if you knew that a person was actually living in an endemic area. Then, of course, when you see a lesion that looks like tuberculosis here in New York City, then of course you expect the fact that this is going to be histoplasmosis in Cincinnati, or at least in the Ohio valley areas.

So that when you look at the films, you can see—if you can know what happens with tuberculosis then you really know what happens with histoplasmosis. So what we'll do today is to show you some of the findings of histoplasmosis, some of the complications, and we'll spend most of the time not so much with the chronic form of histoplasmosis, but a little bit more with some of the acute manifestations, and its variations, and how it sort of differentiates itself a little bit from tuberculosis.

You notice on the slide on this patient, actually, that was presented, you saw this infiltration in the right upper lobe. And if you look very carefully, you would also have seen that the hilar here are also somewhat enlarged, so already we have a focus very similar to the Ghon complex of tuberculosis, parenchymal infiltration, a caseating pneumonia that occurs within the lung—spreads very quickly; actually it's in the lymph nodes. And surprisingly the lymphadenopathy is far greater in involvement in histoplasmosis than—or at least equal—than it does in tuberculosis. In fact, you will find more nodes. And also, interestingly enough, you will find that there is a greater deposition of calcium, actually, not only in the primary focus within

the pulmonary parenchyma, but certainly also within the lymph nodes. Can we go to the slides now, please? Oh, I see. I have to press here. Have the lights out?

And this is just another example of histoplasmosis, showing you the primary focus, and of course this is a look-alike with tuberculosis. Here is your basic parenchymal focus; this is a single one. And of course, you can see that there is a spread and thickening, actually, here, probably lymphangitic spread to the neighboring hilae, which are definitely enlarged. And this is exactly what one would see in tuberculosis.

Histoplasmosis differs a little bit from tuberculosis simply in the fact that there tends to be, by frequency, a greater involvement involving the lung fields than you'll find with tuberculosis. Tuberculosis tends to always have a single focus; histoplasmosis can have multiple foci throughout the lungs. And histoplasmosis, like tuberculosis, will also have severe complications, such as a miliary disease. And I'm not so sure this is very adequately manifested, but if you look very carefully, you can see these little deposits throughout the lung fields. And this, incidentally, is a complication that is also seen in patients that are immunologically suppressed.

And as we said, a more classical demonstration of histoplasmosis is something like you see here, with an overwhelming exposure to the organism, is these multiple infiltrations throughout the lung fields that looks like an overwhelming infection. And surprisingly, very often, these patients are relatively asymptomatic, despite the fact that these lung fields are really full with this type of caseating pneumonia. What happens to these is very simple. They begin to resolve very slowly, and they get a little bit harder. And they can remain as you see here, and they can calcify. So that it is not unusual to see a patient many years later with multiple calcifications throughout the lung fields, looking like miliary calcifications. And these are really miliary histoplasmosis, or multi-nodular forms, actually, of histoplasmosis.

In fact, that used to be said at one time, when one saw these multiple calcifications, that this represented probably old healed miliary tuberculosis, but we know today that this really doesn't exist, actually. Miliary tuberculosis heals over, with very little residual calcification, and therefore if you do see a patient with multiple calcifications throughout the lung fields, the chances are that you're really looking at histoplasmosis. And again, calcifications of the hilar area, far more frequently noted in patients with histoplasmosis than with TB.

Now, since the lymph nodes are very frequently involved, and since the primary focus, actually, is relatively fleeting in many ways, it can disappear and heal over relatively quickly. One may find that there is persistence of disease within the neighboring lymph nodes, just as we see, actually, with tuberculosis. And there was a term applied at one time, called mediastinal granuloma, referring to fibrocaseous lymph nodes within the mediastinum of unknown etiology.

Although nowadays we know, with better bacteriological studies, that the majority of these patients are by far and away related to histoplasmosis, although in a small percentage of cases, these can also be related to tuberculosis. And what we basically see is an entity that also exists, really, in two phases. It presents an acute phase, and in a rather chronic phase. The acute phase, obviously, of mediastinal granuloma related to these enlarged lymph nodes, due to

histoplasmosis, or perhaps tuberculosis. And when it goes into a chronic phase, then we have a fibrosing mediastinitis, which is the exhibit that is presently available to you in the x-ray department.

What do we see, actually, on a radiographic basis is simply lymph nodes. These can be single lymph nodes, and these can be multiple lymph nodes. They may be obvious, and surprisingly, they may not be too obvious. And of course, the majority, or the more obvious ones are that located to the right paratracheal area; we see them in the hilus of curium, or we see multiple variations of what we have just demonstrated.

Radiographically, the most common presentation is a single right paratracheal lymph node, looking very much like you're seeing over here, with very little disease within the pulmonary parenchyma, understandably enough, since very often this is completely healed over. And this can look just like an early sarcoidosis; this can look like a lymphoma, or any disease in which lymph nodes tend to dominate. So you can have your problems here. Sometimes, of course, it's a little bit more extensive, so we have nodes involving the hilum, nodes involving the paratracheal area, the hilum, and sometimes deeply buried within the mediastinum, as you see in this particular patient, who has mediastinal granuloma, or mediastinal histoplasmosis, with very little obvious disease, and sometimes very little obvious clinical manifestations, except for the fact that these patients, when they do have deeply buried lymph nodes, will have them pressing upon their esophagus, and they can present, actually, with dysphagia.

If one looks very carefully—I guess that's going out of focus very quickly—there are some little suggested lymph nodes over there. And on the tomogram—can you focus that please for me? You can see that there are—there's a whole batch of enlarged nodes deeply buried within the mediastinum, displacing the esophagus, and this patient did present only with the simple clinical finding here of dysphagia.

Now the nodes also can extend and involve the pericardium, so that one can be faced with a patient presenting with a pericarditis on the basis of histoplasmosis, with a very simple prodromal period, as you can see over here, nothing to make you suspect the possibility of histoplasmosis, and very similar to what the patient—very similar to that which the patient had today. The differential diagnosis, of course, can be anything with a pericarditis of a viral idiopathic. And of course, if you do have your pneumonic infiltration, if you do have lymph nodes, then you can suspect the possibility that this can be on a granulomatous basis, providing, of course, you can exclude the possibility that this could be on a neoplastic basis.

And there are very few cases actually, up until 1976—very few documented cases, and the reason for that is simply that it is very difficult, obviously, to isolate the organism from these particular patients. And very often, the diagnosis was simply made by an association of events—a complement fixation test, etcetera.

And what do we see? We see a patient who comes in with a pericarditis, but here it's a little bit more obvious in this patient, because we have a classical picture here of histoplasmosis, at least of mediastinal granuloma associated with that, enlarged lymph nodes involving the right

side, a cardiac silhouette that appears to be relatively normal in size. And shortly, this same patient here goes on to demonstrate a very typical picture here of pericardial effusion, and I want you to pay attention to the fact that there is also a pleural effusion associated with this type of event, something that is really unusually seen, actually, in histoplasmosis. For some reason or other, despite the dissemination of histoplasmosis throughout the entire body, which can occur, pleural effusions are relatively infrequent. But they are relatively common, or very common, actually, when you do have—when you do see a patient presenting with a pericardial effusion.

And an analysis of approximately sixteen patients, showing that these are probably not that uncommon, actually, shows that this is a very young disease, as is much of the complications, probably, of acute histoplasmosis occurring in the region of the teenage, early twenties. The fluid is usually hemorrhagic. And of course, in all these patients, the complement fixation is positive.

What is interesting, and what has not been proven but what is suggested, of course, is the pathogenesis. It is believed, like in tuberculosis, that the nodes can actually break into, or associate themselves with the pericardium, exciting a pericardial effusion. But what is more or less accepted nowadays is the fact that there may be a hypersensitivity response here, because of the presence, actually, of the pleural effusion, and because of the delayed onset of this simple situation. The pericardial—the pleural effusions, as I said before, are very rarely seen in histoplasmosis, except when one has a pericardial effusion.

As in tuberculosis, the mediastinal nodes can actually erode, actually, into the bronchus, excite an endobronchial disease, and of course, wind up with a diffuse involvement or atelectasis of the involved bronchus. This patient here, we begin to see decreasing in volume on the left side. Notice the shrinkage here of the ribs. Note that there is absolutely obvious loss of volume. And of course, within one day later there is complete atelectasis of the left lower lobe—left upper lobe, rather, despite the fact that you see that up there, and of course, on bronchoscopy, histoplasmosis was taken off from a definite granuloma within the left upper lung field.

Superior vena cava is a not uncommon complication, actually, of mediastinal histoplasmosis, both in the acute phase and as well as within the chronic phase. And this is quite understandable. The vein is, obviously, a compressible item, and if one eliminates the more common causes of superior vena cava syndrome, such as neoplastic diseases like carcinoma and lymphoma, one will find that histoplasmosis is probably the next most common lesion, or at least the most common benign cause of a superior vena cava syndrome.

And another interesting finding that we see with histoplasmosis or histoplasmose is that they do grow, which is very unusual, very interesting. And this apparently also accounts for the fact of—or at least for the production of the fibrosing mediastinitis. And this has been called the benign progressive nodular histoplasmosis, and the pathogenesis here, as suggested by Goodwin and Snell is that there is a hypersensitivity type of response. Some antigen, apparently, is secreted from the caseating substance, through the granuloma to the outside, exciting, of

course, the tissues around this, producing a lot of fibrous tissue, and therefore they tend to grow not by caseation, or not by necrosis, but by apposition, actually, of fibrotic tissue around the area of involvement.

And we see this in this medical student, where he has this right paratracheal node in 1974 due to histoplasmosis. And three years later, we can see where this node is actually almost doubled in volume, and that there is a little bit more extension in the region of the mediastinum. And here, on a tomogram, we can see the size of this, and the calcifications present within the node that is so typical also with histoplasmosis. And this apparently also suggests, and accounts for, the production of fibrosing mediastinitis, that is, the nodes never heal; excite all this diffuse fibrosis around the area, accounting for all these various changes that can be relatively deadly. And we have a whole exhibit of this, I said, downstairs in the X-ray Department, so we won't talk any further about this.

And I'd just like to show you a chronic—two chronic pictures of histoplasmosis. And you can see that they are really exactly like some form of advanced tuberculosis, and they do look exactly alike. You have diffused fibrosis throughout the lung fields, nodularities, calcification, and you can even—well, it's not very typical over here, clearly seen, but huge cavities that are present here within the upper lung fields. Okay. Thank you. [Pause]

MODERATOR: I want to thank Dr. Rabinowitz for really a very complete survey of the radiologic findings. I just want to say a few words about this patient. This patient did have hairy cell leukemia, and just if one looks at the infections in patients with hairy cell leukemia, they really break down to about fifty percent bacterial infections, and the other half, non-bacterial infections, which include mycobacterial infections and fungal infections. There seems to be an increased incidence of mycobacterium kansasii infections in these patients. And of course, there are the fungal infections, which include Cryptococcus, and histoplasmosis has also been described.

I'll just say a few words about how I think this patient was infected with histoplasmosis, and like so many other diseases, that is, infectious diseases, one really has to deal with excreta. In this case, it is avian excreta that one is concerned with, whether they be pigeons, blackbirds, or chickens, actually. And in fact, there are many reported outbreaks of histoplasmosis in people who deal—who clean chicken coops, or deal with chickens. In fact, the chickens can carry this organism on their feathers, and there's a famous case of histoplasmosis in a child who innocently was sent a pillow made by a grandparent stuffed with feathers from the farm, and these feathers had histoplasma spores on them, and the child came down with acute histoplasmosis. Now, can I have the first slide please?

This just goes to show you where you shouldn't move, if you're thinking of leaving Mount Sinai. This area in white here—it's actually black in the picture—is where the heaviest concentration of histoplasmosis is in this country. And if you look in upstate New York, you can see that there are pockets of histoplasmosis there. This doesn't mean that there is no histoplasmosis where it looks sort of clean. It just means that there's—that there's enough there

to measure it. Actually, there probably is histoplasmosis all over the country. All you have to do is have contact with the birds. The concentrations in soil here are much greater in the area shown in white. Now this patient actually visited the stalls in Acapulco, and he made a point of going to the chicken stalls, where they had these big chicken coops, and he may have got his histoplasmosis there. May I have the next slide, please?

This is just a classification of histoplasmosis. Now, there's an important point to be made here, which has recently been emphasized by Goodwin and his co-workers in Nashville, Tennessee, and published in a paper in *Medicine* in the July issue. And that is that there is a fundamental difference in the pathogenesis of histoplasmosis and tuberculosis. The term primary infection in histoplasmosis is really not appropriate. What it is—it's an acute infection. There is no chronic lingering intracellular phase, as there is with tuberculosis. In tuberculosis, we speak of primary infection and reactivation. In histoplasmosis there is a waning of the immunity over years, so that someone can be re-infected with the organism. And this is probably what happens to those who have been infected in childhood, may have had symptomatic, or asymptomatic histoplasmosis, and then can later on in adulthood, if they are still in an endemic area, and they get enough of an inoculum, they'll be infected all over again. So this is the acute pulmonary histoplasmosis, and I think Dr. Rabinowitz covered this.

The patient we have here is really an example of disseminated histoplasmosis in a patient with an immune defect—probably a T-cell function defect, because we know that neonates and the very young are much more susceptible to histoplasmosis, even if the inoculum is low. What determines whether a patient develops asymptomatic or symptomatic infection primarily is the size of the inoculum. In other words, the more spores breathed in, the greater the chance of symptomatic infection. And of course, there is the chronic pulmonary histoplasmosis, which has to do with patients who already have structural defects in the lung, such as emphysema bronchiectasis. I'm not going to show the next slide. I just want to say a word about therapy, because the therapy used in this patient—may I have the lights, please?

The therapy used in this patient was a combination of Amphotericin B, and a new drug, ketoconazole. Now, ketoconazole is a new imidazole like miconazole, but it is soluble, so that it can be absorbed through the gastrointestinal tract. And doses of 200 to 400 milligrams give rise to about two to four micrograms per ml in the blood stream, which is a therapeutic level. Now, this drug does have activity against coccidiodomycosis, para-coccidiodomycosis, chronic mucocutaneous candidiasis, and is really a good drug for the treatment of the dermatophytic infection. The drug is relatively non-toxic. We decided to give this patient ketoconazole on the basis of the findings of in vitro studies that this drug was active against histoplasmosis. At the time we gave him the drug, we had no idea that this drug had any activity in patients. But as I said, the drug was relatively non-toxic.

It turns out that there's recently been a paper in the October issue of the *Annals of Internal Medicine*, where four patients were reported, also who had underlying diseases, and they had disseminated histoplasmosis, who were treated with ketoconazole from ten to twelve months without any side effects, and with apparent success, except in a patient who had it in an aortic aneurysm that had to be resected. So that it looks like the therapy for disseminated

histoplasmosis will be a combination of Amphotericin B, given over a short period of time—meaning anywhere from four to eight weeks—and completing the therapy with a long course of ketoconazole.

What we don't know now is whether this drug will be useful in the treatment of central nervous system infection. We just don't know that. I would rather doubt it, because I don't think one is going to get enough of the drug into the central nervous system. But in any event, I think this is an exciting advance, because we now have a relatively non-toxic drug that can be given orally for a long period of time, so that patients can be released from hospital earlier, and essentially treated at home.

This patient, by the way, has done very well, as a patient of Dr. Wisch's [Nathaniel Wisch], has followed him, and he has really done very well in the several months since he's been released from the hospital.

Now, the next case is a very interesting one, which we will not see too often in New York City, but maybe more often than other places, because we do have a population that does carry parasitic diseases. And this infection is the hyper-infection syndrome, as it's called, due to strongyloides stercoralis. Now, we are fortunate this afternoon to have a visiting speaker from Boston—everybody wants a visiting speaker from Boston. Dr. Massey [?] came to us about a year and a half ago, from Boston, where he was chief resident at the Boston City Hospital. Since Dr. Massey did make this diagnosis in this patient on clinical grounds alone, I felt that it would be fitting that he not only present the case, but also give the discussion of the case. [Pause]

MASSEY: This is patient [*initials deleted*], a sixty-seven year old Puerto Rican female who was admitted on November 5th with fever and an exacerbation of her asthma. She'd been discharged from Metropolitan Hospital several days earlier, where she had also been hospitalized for an asthmatic attack. Her past medical history was significant for her asthma, which she had for many years, and had been steroid dependent for the previous year, and hypertension. And her medications on admission were prednisone, 30 milligrams a day, and theophylline. Her social history is that she was born in Puerto Rico, and had left there at age ten, living in New York City ever since.

The physical examination on admission revealed a lethargic woman in marked respiratory distress, temperature 103. The rest of the vital signs you see there. The skin was normal, no lymphadenopathy. Her chest revealed diffuse wheezes throughout all the lung fields; her heart, a two over six systolic ejection murmur. The abdomen was non-tender, otherwise normal. Her extremities and joints were normal, and neurologically she was extremely lethargic but without any focal abnormalities. The laboratory data on admission: you can read there that significant pieces of the chest x-ray were normal. The arterial blood gas on room air was ph 7.22, PCO_2 of 55, PO_2 of 45, and the white blood cell count of 12,600, with 80 polys, six bands, six lymphs, three monos and five metas.

The hospital course: the patient was intubated shortly after admission and was begun on parenteral bronchodilators and high dose corticosteroids. Over the next several days, her chest x-ray developed bilateral interstitial infiltrates. Could I have the first slide please? [Pause] This is her chest x-ray on admission. And [pause] this is a representative film from later in her course. Her x-ray looked like this from about two days following admission, for the next three weeks. The sputum gram stain showed polys and mixed gram positive and gram negative flora. Swan-Ganz pressures were consistent with non-cardiogenic pulmonary edema. And she was begun on clindamycin and tobramycin for possible bacterial pneumonia, and increasing levels of respiratory support were necessary.

Her course was complicated by persistent fevers with intermittent hypotension, and several episodes of documented bacteremia with single or multiple isolates. And the organisms that were isolated were Serratia marcescens, Enterobacter cloacae, and E. coli, despite various broad spectrum antibiotic combinations. Sputum AFB stains were negative, and gram stains and cultures continued to show a variety of organisms including the ones isolated from the blood. The patient was continued on high-dose parenteral corticosteroids. She became progressively obtunded without any focal neurologic abnormalities, and developed a ten-centimeter right upper quadrant mass without any change in her liver function tests.

The remainder of the work up included a spinal tap, which had ten lymphs, no red cells, protein of 69, glucose of 117. Cultures, counterimmunoelectrophoresis, and [unclear] stains were negative. Her KUB was consistent with ascites. Urine cultures grew Candida albicans repeatedly. Stools and duodenal aspirates were over and parasites were negative. A CAT scan of the head [pause to change slides] showed a three centimeter enhancing lesion in the right vertex.

On the twenty-second hospital day, bronchoscopy and transbronchial biopsy were performed [pause to change slides] and this was what was seen in her bronchial washings. This is a phase micrograph of a rhabditiform larva Strongyloides stercoralis. These were also seen. These are healthy eggs of Strongyloides. And once these eggs were seen, the people in the lab made an exhaustive search of all the specimens and found an adult [pause to change slides]. And as far as we know, adults had never been described in the lung before.

The patient was treated with thiabendazole, a gram and a half per NG tube, twice a day. Twelve hours after receiving the first dose, she became febrile to 105, hypotensive, and developed atrial tachycardia. She stabilized spontaneously, however, defervesced, and the thiabendazole was continued for eleven days. During that period, she remained afebrile and blood cultures turned negative. Her respiratory status improved dramatically, as did her neurologic status. The right upper quadrant mass resolved before it could be worked up. A CAT scan of her head is yet to be repeated. Chest x-ray, the most recent film [pause to change slides], has cleared dramatically. And what she now has in her sputum, persistently, are these [pause to change slides], which are damaged eggs of Strongyloides. You can see the irregular membrane. No more larva and no more adult worms are being seen.

Now, let me quickly try to discuss the hyper-infection syndrome. First, this is a slide of the lifecycle of Strongyloides. It's a very busy slide, but let me point out a few interesting features. If you start in the upper right hand corner, that's the rhabditiform larva, the free-living larva of Strongyloides. And from that stage, the organism can do three different things: it can live without a human host, just live in the soil. It matures from the rhabditiform larva into free-living adults; lays eggs; they hatch into more rhabditiform larva, etcetera. It doesn't need a human host.

The usual parasitic cycle occurs when it molts from a rhabditiform larva into a filariform, or infective, larva. And it invades the skin, usually the skin of the foot; gains access to the systemic circulation, goes to the lungs, to the alveolar spaces, to the tracheal-bronchial tree, the trachea, the glottis, where it's swallowed. All this time it's molting into an adult. It finally finds its way into the proximal jejunum and distal duodenum, where the male and female adults mate. The male is passed in the stool; the female lodges in the mucosa and starts laying eggs. So the usual parasitic infection lasts the lifespan of an adult female, which is a few weeks to a few months.

One of the—the thing that's unique about Strongyloides is the third thing it can do, which is the so-called auto-infective cycle. And that occurs when rhabditiform and filariform larva form within the lumen of the gut, instead of just rhabditiform larva, which are then passed in the soil, invasive filariform larva form within the body. So they invade the wall of the gut, gain access again to the systemic circulation, go to the lungs, etcetera, etcetera. And the significance of that is two-fold.

One, it allows the infection to persist well beyond the lifespan of the adult female. In fact, it's been documented to persist as long as 30 years, and this case may very well have persisted for 57 years. It also has the potential for increasing the parasite load geometrically, with each cycle. And that potential leads us to the hyper-infection syndrome, which is a rare, probably under-diagnosed syndrome, where because of enormous numbers of filariform larva forming in the gut simultaneously, and a defect in cell-mediated immunity, there's massive simultaneous invasion of multiple organ systems, and an explosive disease with septic course, usually fatal.

The symptoms of Strongyloides infections, in uncomplicated infections, fifty percent of patients are asymptomatic. When there are symptoms, they're very vague and non-specific: some crampy abdominal pain, occasionally some diarrhea but usually not, mild anemia, occasionally a little bit of weight loss. In more severe infection, malabsorption can occur, as well as recurrent wheezing, which represents the auto-infective cycle going through the lungs. And it's been put forth as a cause of some patients' asthmatic attacks.

The hyper-infection syndrome usually presents, as I said, as an explosive, impressive illness, with unexplained bacteremia, often unexplained meningitis, in the setting of multiple system failure. The pathology that's been found in these patients ranges from normal to small bowel edema, secondary to lymphatic obstruction by the larva, to ulcerations, to a sprue-like

picture, and to frank perforations in the gut. The hyper-infection syndrome has been recognized for about the past twenty years.

And the review of the literature, the English language literature, on this entity in the last twenty years comprises 103 cases, and that's reference number one in the bibliography. In those 103 cases, eighty-nine of the patients were immunocompromised in one way or another, and fourteen were normal. The epidemiology of this disease: it has a slight male to female predominance. It's almost always been reported in adults. There are only one or two cases in children. The geographical distribution of Strongyloides is throughout the tropical and subtropical regions of the world. There are areas of the United States which are endemic, particularly Florida, Louisiana, and the Appalachian areas of Kentucky and Tennessee.

There are seventeen cases of patients who have acquired the infection within the United States, but there are only three cases of patients who seemed to have acquired the infection within non-endemic areas, all of whom were patient—were people who worked in institutions. Two were nurses and one was a man who changed bed linen. There are many reported cases, however, of patients presenting with the hyper-infection syndrome who apparently acquired their original infection many, many years earlier in an endemic area, like our patient seems to have acquired it.

The predisposing factor seemed to focus on a defect in cell-mediated immunity. And the evidence for that is in an autopsy series, which is reference number four in the bibliography, in which a lack of granulomatous response was found around larva invading tissue, and decreased lymphocytes in the thymus and in thymus-dependent areas in the lymph nodes and spleen was found. The syndrome has been reported in a wide variety of predisposing conditions, supposedly predisposing conditions, including alcoholism, nephrotic syndrome, transplant patients, lupus, and asthma. About fifty percent of the patients have had non-malignant conditions like those; the other fifty percent have had primarily hematologic malignancies—virtually all of them, in fact.

But the final common pathway seems to not be the underlying disease, but the therapy which the patient is receiving. Every single one of the patients in the literature who had a non-malignant disease was on prednisone. And only six of the patients out of thirty-five were on any other immunosuppressive therapy. Two-thirds of the cancer patients were on prednisone. So, steroids, or prednisone—[Pause in recording]—promote invasion by the filariform larva, but they also—they also speed up transformation from rhabditiform into filariform larva within animal GI tracts. So there's fairly good evidence that steroids have a unique effect on Strongyloides, as well as on the host, toward promoting the hyper-infection syndrome.

In some of the compromised patients in the autopsy series, severe protein malnutrition and extensive small bowel disease was found, so it's conceivable that Strongyloides itself can be the underlying condition which predisposes to the hyper-infection syndrome. In other words, if you carry the parasite long enough, and develop enough mucosal abnormalities to cause severe enough protein malnutrition, you'll get a cell-mediated immunity problem, and predispose yourself to the hyper-infection syndrome.

The syndrome begins when extraintestinal organs are involved, and the lung is the most frequent organ involved. And the findings have been asthma, in most of the cases, opacities, consolidation, lobar pneumonia, and as in this patient, diffuse or focal interstitial infiltrates. In every patient who's been autopsied, who had lung involvement, there was also other organ involvement. And the other organs involved had been abdominal nodes, liver, spleen, pancreas, thyroid, kidney—there have been larva reported in the urine—and central nervous system has been reported in three patients. And our patient may very well have central nervous system involvement with that CAT scan you saw.

There's only one other case of a brain itself being invaded by larva that's been documented. That patient died, and the documentation was by autopsy. And the lesions in that patient were caused by micro-infarctions caused by larva lodging in capillaries, primarily in the cerebellum, as well as by large granuloma formation around degenerating larva. And if you had to pick a lesion that that CAT scan resembles, it's a tuberculoma, and that could be an actual granuloma forming around a degenerating larva in this patient.

The mortality of this condition is 77 percent in compromised patients, about 43 percent in the uncompromised patients, and the usual cause of death is secondary infection. Virtually every one of these patients—I'll give you the numbers—twenty-five out of thirty patients who presented with bacteremia have died. And the clues to the diagnosis are in the nature of the bacteremia. It's almost always unexplained, and with enteric organisms. There's an old pearl in infectious disease that it's with multiple isolates, and that has been seen in a few cases, but the key is that it's with enteric organisms, when there's no obvious reason for the patient to have bacteremia with those organisms.

The reason that this happens is that worms themselves, for one thing, have GI tracts, so when they penetrate the gut and get into the blood, they're carrying their own organisms into the blood with them. Two, they're carrying organisms from your own gut into your blood, because they're piggybacking on the larva as they pass through the wall of the gut. And three, there are mucosal ulcerations and frank perforations seen in severe Strongyloidiasis, anyway. The diagnosis is extremely difficult. It requires a high-index of suspicion. Because the early symptoms are vague and often absent, there's often no eosinophilia at all in the hyper-infection syndrome, where eosinophilia is one of the hallmarks of uncomplicated Strongyloidiasis. The lack of the eosinophilia, as was seen in this patient, is an extremely poor prognostic sign. The stools are negative for ova and parasites in 25 percent of the patients, and these duodenal aspirates are even negative in 10 percent. And this patient had multiple negative stools and duodenal aspirates before the diagnosis was made.

There are skin tests and serologic tests for Strongyloides, but they have little clinical correlation, and even the CDC, which does the serology, doesn't put any stock in it. So the keys are high index of suspicion, and in a patient who presents with unexplained enteric bacteremia, and unexplained pulmonary infiltrates transbronchial biopsy should be done, or at least bronchial washings, because there's an extremely high yield of isolating the larva that way.

The treatment is with thiabendazole, which has been used successfully in twenty of these cases. And 70 percent of patients who live long enough to get two days-worth of thiabendazole have survived. We treated this patient with the maximum dose, which was 25 milligrams per kilogram, BID, for ten days, but regiments ranging from two to fifteen days have worked. Relapses, however, have been reported, particularly in patients in whom the immunosuppressive therapy couldn't be stopped, as in this case. The side effects of thiabendazole are mostly subjective, with nausea and dizziness, and occasionally more severe side effects—hypotension and arrhythmias occur. And one interesting side effect, which was probably what this patient had twelve hours after the therapy was started, was a Herxheimer reaction, similarly to what's seen in secondary lues because of massive release of endotoxin. This patient was treated with thiabendazole; you can speculate that there was a massive killing of larva, and toxins were released, causing this septic-looking episode that she had.

Because of the lesion on CAT scan, we were forced to investigate whether thiabendazole gets into the spinal fluid and brain or not. There's very little evidence that it does. There's only one case report that the company has of a boy treated for eosinophilic meningitis with it, and he got sub-therapeutic levels with maximum doses. But nevertheless, thiabendazole is virtually the only drug that works for this. Mebendazole has been used in a few treatment failures. Another issue in this patient is whether prophylactic thiabendazole should be instituted, since she has not been able to be weaned off her steroids completely, and still has this ominous lesion sitting there on CAT scan, and a few of these damaged eggs sitting in her lungs.

I just want to close by mentioning one case report. It's one of the historical case reports on Strongyloides. This came up, because when the diagnosis was first made, the nurses in the ICU very appropriately asked us if they could catch Strongyloides from this patient. And we frankly weren't sure. There is a case report of a derelict alcoholic, who worked changing bed linens in a flop house on the lower East Side, and was admitted to Saint Clare's Hospital in the early 1960s with pulmonary infiltrates, diarrhea, high fevers. And three or four days into his hospital course, larva were found in his sputum and stool. He was treated with thiabendazole. But he had never been in an endemic area—he came from northern Europe and never traveled outside of there and New York City, and apparently had acquired the infection by handling soiled linens. So after reading that, we told the nurses to be careful and wear gloves. But as far as we know, no one has come down with it yet. Are there any questions? Thank you. [Pause]

[Lengthy unclear comment from audience]

MASSEY: Right…Oh, absolutely.

[Commenter continues]

MASSEY: Yeah. It seems to be an important risk factor, but only half of the patients who have had the hyper-infection syndrome have been eosinopenic. Most—the other half have had eosinophil counts consistent with a Strongyloides infection. So it seems to be a risk factor, but not the sole risk factor, immunologically. But, we've wondered when we're going to see our first homosexual male come in with this. I think it's something we have to keep in the back of our minds. Any other questions?

MODERATOR: If there are no other questions, I thank our speakers. [Applause]

[End of recording]