
Family Practice Grand Rounds

Generalized Lymphadenopathy and Fever of Undetermined Origin

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DR. JOHN DOCKUM (*Second year family practice resident*): A 25-year-old white man was in his normal state of good health until four days before hospital admission, when he developed fever, chills, and abdominal discomfort. When first seen in the office, examination revealed generalized muscular and lymph node tenderness and right lower quadrant tenderness. White blood count was 5,100/cu mm with 36 percent neutrophils, 24 percent bands, 24 percent lymphocytes, 6 percent monocytes, and 8 percent eosinophils. Urinalysis showed 1+ protein with no cells. Over the next two days he developed increasing headache, photophobia, sore throat, and a stiff neck. He was admitted to the hospital with a differential diagnosis of (1) severe viral syndrome, (2) streptococcal pharyngitis, (3) mononucleosis, and (4) meningoenzephalitis (viral vs bacterial).

Physical examination on admission revealed temperature 100.8 F; pulse, 80 beats per minute; respirations, 30 per minute; and blood pressure, 114/64 mmHg. Positive physical findings included scalp tenderness, a minimally injected pharynx, tenderness of the posterior neck muscles on extreme flexion, tender posterior cervical nodes, tender axillary and inguinal nodes bilaterally, tender musculature in the abdominal wall, and photophobia on neurologic examination.

Admission Laboratory Findings

Throat culture for beta hemolytic streptococcus and a Monospot test were negative. The white blood count was 6,300/cu mm (55 percent lympho-

cytes, 29 percent neutrophils, 10 percent bands, and 6 percent eosinophils) and the hemoglobin was 15.0 gm/100 ml. The urinalysis was normal and the VDRL was nonreactive. The chemistry panel was within normal limits, except for lactic dehydrogenase (LDH), which was 259 units/100 ml (normal 85 to 172 units/100 ml) and alkaline phosphatase 36 units/100 ml (normal 9 to 35 units/100 ml).

Shortly after admission lumbar puncture was performed. Cerebral spinal fluid analysis revealed lymphocytes 3/cu mm, clear colorless fluid, lactic acid 7.0 mg/100 ml (normal less than 24 mg/100 ml), glucose 54 mg/100 ml, protein 34 mg/100 ml, normal Gram stain, and negative routine and viral cultures (reported later). Chest x-ray examination performed after admission revealed a new mediastinal mass in the left hilum (Figure 1).

Hospital Course

Through the first week of hospitalization the temperature reached daily peaks to 102 F. Further evaluation revealed nonreactive mumps and tuberculin (PPD) skin tests and negative blood cultures (repeated three times). Repeat urinalysis was normal, repeat Monospot negative, LDH-3 isoenzyme 37 percent (normal 20 percent), hepatitis B surface antigen negative, toxoplasmosis titer within normal range, febrile agglutinins within normal range, sedimentation rate 37 mm, serum glutamic oxaloacetic transaminase (SGOT) 80 units/ml, repeat alkaline phosphatase 42 units/100 ml and serum glutamic pyruvic transaminase (SGPT) 104 units/ml (normal 3 to 36 units/ml). The patient's generalized adenopathy persisted and was quite tender.

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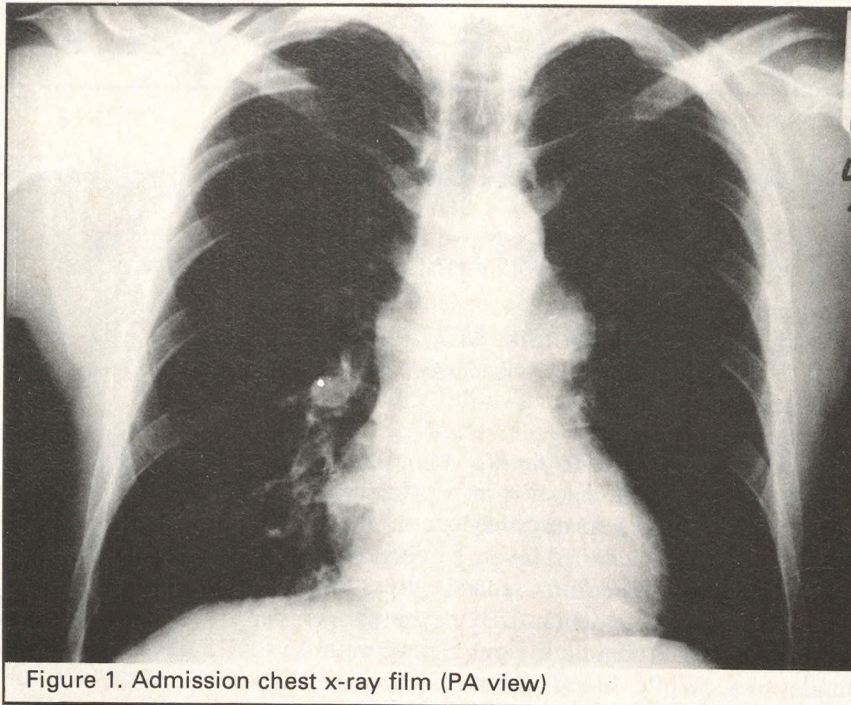


Figure 1. Admission chest x-ray film (PA view)

Surgical consultation was obtained for cervical node biopsy five days after admission. Results were interpreted as "reactive" and nondiagnostic for malignancy or granulomatous disease. Culture and imprint of the node were negative. Following the biopsy, the patient's temperature continued spiking to 102 F with profuse night sweats. Three days following cervical node biopsy, mediastinal node biopsy was performed. This revealed a large mass at the aortic arch with a histology consistent with Hodgkin's disease of the mixed cellularity type.

Staging workup included the following: bone marrow biopsy, within normal limits; computerized tomography (CT) of the abdomen, within normal limits; and lymphangiogram revealing a suspiciously large periaortic node at the L-3 level. Subsequently, the patient underwent laparotomy. This revealed an enlarged spleen not pathologically involved with Hodgkin's disease, liver biopsy revealing no Hodgkin's disease, and sections of upper abdominal periaortic nodes revealing Reed-Sternberg cells consistent with Hodgkin's disease. The patient was judged to be stage 3-B. Following recovery from surgery, combination chemotherapy was begun with the four-drug MOPP regimen (nitrogen mustard [Mustargen],

vincristine sulfate [Oncovin], procarbazine hydrochloride, and prednisone).

DR. J. CHRISTOPHER SHANK (*Assistant Director, Residency Program*): I had gotten to know this man and his family over the last two years in the Family Practice Center. His illness developed into a very interesting and challenging problem in more ways than one. I would like to discuss some of the aspects of the case as it presented initially in the office. Then I will offer some comments about the initial differential diagnosis of generalized lymphadenopathy. Finally, we will discuss the differential diagnosis and diagnostic approach to a fever of undetermined origin.

Let us go back and review the presenting symptoms of this patient. He came to the office with three days of abdominal pain and fever. Initially I considered appendicitis. He had no rebound tenderness, and his blood count was unremarkable at 5,100/cu mm; thus the most likely office differential reasonably included viral gastroenteritis, mesenteric adenitis, and parasitic infection (because of a slightly elevated eosinophil count). We elected to follow him as an outpatient. Over the next two days the abdominal pain lessened, but he began to complain of severe throbbing headaches, diffuse myalgias, arthralgias, and sore throat. He also

Table 1. Causes of Generalized Lymphadenopathy

Drug Reaction
Systemic Infection
Bacterial
Tuberculosis
Subacute bacterial endocarditis
Brucellosis
Secondary syphilis
Fungal
Coccidioidomycosis
Histoplasmosis
Viral
Hepatitis
Mononucleosis
Coxsackie virus
Cytomegalovirus
Parasitic
Toxoplasmosis
Immunologic
Immunoblastic lymphadenopathy
Collagen vascular disease
(eg, lupus erythematosus)
Malignancy
Hodgkin's disease
Non-Hodgkin's lymphoma
Leukemia
Metastatic carcinoma
Other
Sarcoidosis
Hyperthyroidism

complained of photophobia with neck stiffness. The remarkable finding on his physical examination was diffuse tender adenopathy. This changed my differential diagnosis to include a generalized viral syndrome, perhaps a severe streptococcal syndrome with pharyngitis, or mononucleosis. Of course, we were also worried about meningoen- cephalitis, either viral or bacterial. With the latter being a possibility, he was admitted to the hospital, whereupon the spinal fluid was found to be unremarkable. However, the admission chest x-ray film was revealing of a fullness in the pulmonary outflow tract region. This was consistent with mediastinal adenopathy. Thus we faced the problem of generalized lymphadenopathy.^{1,2} The differential diagnosis for this problem is illustrated in Table 1. With any unusual medical problem, it is important to consider a drug related etiology. The patient had no history of drug ingestion. Under the next major category in Table 1 (systemic infection)

are listed the common etiologies that were high on our list of possibilities. We strongly considered a systemic bacterial infection or a severe viral syndrome as well as tuberculosis, syphilis, hepatitis, mononucleosis, and toxoplasmosis.

The immunologic causes seem remote, but the possibility of malignancy affecting our patient was quite high. Our continued medical workup, as outlined above, was unrevealing. And thus the patient approached the classic criteria of Petersdorf and Beeson for a fever of undetermined origin: (1) an illness of at least three weeks' duration, (2) intermittent fever to 101 F or greater, and (3) at least one week of hospital based investigation.³ These criteria have been liberalized to include an illness duration of less than three weeks, such as our patient with two weeks' duration, and a less strict requirement for the one week of inpatient hospital investigation. Practically, much of the initial workup can be done as an outpatient.

At any rate, the broad based differential diagnosis presented initially by Petersdorf and Beeson and more recently reviewed by several authors, including Jacoby and Swartz, and Cross, was considered at that point in our patient's evaluation.^{4,5} As is shown in Table 2, which presents a practical outline of the traditional causes for fever of undetermined origin, infections cause about 40 percent of cases. For our patient three sets of blood cultures were negative. It is interesting to note that many of the conditions in Table 2 also exist in Table 1.

The second major cause for fever of undetermined origin are the neoplasms, which traditionally cause 20 percent of cases. Common tumors include lymphoma, Hodgkin's, leukemia, hypernephroma, and metastatic liver disease. The third major category covers collagen vascular diseases (15 percent), which seemed unlikely in our patient. The fourth category is extremely important, accounting for 15 percent of cases. This miscellaneous group includes pulmonary embolus, drug fever, inflammatory bowel disease, and factitious fever. Traditionally, 10 percent of cases of fever of undetermined origin have no diagnosis found.

Table 3 summarizes six papers from different settings regarding this topic. The traditional university setting case series in columns 1 and 2 compared with two series from community hospitals in columns 3 and 4 and with two pediatric/elderly series in columns 5 and 6. Note that there was a

Table 2. Causes of Fever of Undetermined Origin**Infections** (40 percent)*Common*

- Tuberculosis (military)
- Hepatobiliary infection (including cholangitis, liver abscess, empyema of gallbladder, subhepatic abscess)
- Subacute infective endocarditis
- Other intra-abdominal abscess
 - Pancreatic
 - Tubo-ovarian
 - Subphrenic
 - Paracolic
 - Appendiceal
- Urinary tract infection
 - Pyelonephritis
 - Renal carbuncle
 - Perinephric or prostatic abscess

Less common

- Brucellosis
- Toxoplasmosis
- Psittacosis
- Cytomegalovirus infection
- Meningococcemia
- Gonococcemia
- Spirochetal infection (leptospirosis, syphilis)
- Mononucleosis
- Disseminated mycoses (histoplasmosis, cryptococcosis)

Neoplasms (20 percent)*Common*

- Lymphoma and Hodgkin's diseases
- Leukemia
- Hypernephroma
- Metastatic liver disease
- Gastrointestinal especially hepatoma

Less common

- Breast
- Brain

Collagen Vascular Disease (15 percent)

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Late onset juvenile rheumatoid arthritis (Still's disease)
- Temporal arteritis
- Rheumatic fever

Miscellaneous (15 percent)

- Pulmonary emboli
- Drug fever
- Inflammatory bowel disease
- Factitious fever
- Sarcoidosis
- Hypersensitivity state

Undiagnosed (up to 10 percent)

much higher percentage of cases due to infection (52 percent) in the pediatric series; also there was a higher percentage of cases due to neoplasm and connective tissue disease (24 and 26 percent) in the elderly series.

Finally I want to spend a few minutes discussing a general diagnostic approach to the fever of undetermined origin. The literature is replete with sophisticated algorithms for dealing with this complex clinical problem. Vickery and Quinnell stated, "Few other syndromes give rise to such a wide variety of possible diagnoses, and therefore, offer as much potential for ineffective use of the laboratory."¹⁰ Murray stated, "Indeed students, house officers, and attending physicians alike tend to view these cases as rather unique opportunities to unleash their full complement of clinical and laboratory skills."¹¹ But keeping us in line with our family medicine philosophy, Esposito and Gleckman suggested the following: "In addition to orchestrating a rational and thorough diagnostic evaluation, the physician must assist the patient and family in coping with the stresses associated with a prolonged hospitalization and an uncertain diagnosis. The importance of compassion and common sense in the management of these patients must not be forgotten."¹²

After reviewing several articles, I believe Dr. Allan Cross has offered the most practical approach for the family physician to follow.⁵ He has stated, "The tempo of your workup should be dictated largely by the condition of the patient proceeding from the safest, least invasive manipulations to those procedures with increased risks." The family physician must use common sense and not be locked into an algorithmic approach in a fever of undetermined origin. Cross suggested approaching the problem in three phases. Phase 1 includes a careful history and physical examination, withdrawal of all drugs not absolutely necessary, ruling out factitious fever, and then an initial laboratory examination. This would include basic culturing of body fluids, basic hematologic and serologic evaluation, and a chemistry examination for liver function. Radiologic studies in phase 1 include a chest x-ray examination, intravenous pyelogram, and a liver/spleen scan. Acute phase serum should be frozen for future viral studies, and perhaps most importantly, a directed biopsy at any abnormal node or skin lesion should be performed early on.

Table 3. Fever of Undetermined Origin: Literature Series

	Petersdorf and Beeson ³	Jacoby and Swartz ⁴	Howard et al ⁶	Gleckman et al ⁷	Pizzo et al ⁸	Esposito and Gleckman ⁹
Year	1961	1973	1977	1977	1975	1978
Setting	University hospital	University hospital	Community hospital	Community hospital	Pediatric	Elderly
Number of patients	100	128	100	34	100	111
Infection (%)	36	40	37	18	52	36
Neoplasm (%)	19	20	31	9	6	24
Connective tissue (%)	15	15	19	9	20	26
Miscellaneous (%)	23	20	8	29	10	9
Undiagnosed (%)	7	5	5	35	12	5

Phase 2 would include more sophisticated microbiologic and serologic evaluation. Blind tissue biopsy of the liver, bone marrow, or temporal artery would be considered. A secondary level of radiologic tests would include lung, bone, or gallium scans, a sinus and gastrointestinal x-ray series, lymphangiogram and/or an abdominal CT scan.

Should phase 2 tests prove unrevealing, Cross includes the following four possible steps in phase 3: (1) observation over time, (2) peritoneoscopy, (3) laparotomy, and (4) trial of therapy.

In conclusion I offer the following clinical observations gleaned from the literature. Most cases of fever of undetermined origin are caused by atypical presentations of common illnesses rather than obscure diseases. "Once is not enough" applies to taking a meticulous history and physical examination and to obtaining multiple biopsies, even of the same body tissue. Most diagnoses are made by acquiring tissue for microbiologic or histologic examination. Cases of fever of undetermined origin that are still undiagnosed after an extensive workup (and especially where there is no weight loss) have a favorable prognosis.

I would be happy to respond to any questions.

DR. CARL ASCHOFF (*Director, Residency Program*): What has occurred in follow-up with the patient presented?

DR. SHANK: Unfortunately, my patient exhibited a great deal of denial, anger, and depression in the weeks following his diagnosis. He was poorly compliant in attending the oncologist's office for chemotherapy cycles, receiving only four or five MOPP cycles. He was frequently sul-

len or hostile with his wife, creating extreme tension in the family, which includes two small children. Despite invitation and encouragement, he was hesitant to discuss his feelings. And yet remarkably, in spite of an incomplete chemotherapy program, he has entered remission and the family unit has maintained its integrity.

Thus in summary, this case is presented as an example of a challenging organic problem for the family physician. However, its aftermath of personal and family stress illustrates the equally challenging emotional aspects present with most serious illnesses.

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