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A Grandma with Two Years of Fever and Agony

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Abstract : A 72 year old woman living in Namuen District, Nan Province, was referred from a local hospital for having two years of fever and back pain. Her symptoms started with feeling malaise, intermittent fever with chills and body ache. All the symptoms got worse at night making her unable to sleep. She also experienced back pain all day and night in additon to anorexia. She had no cough, petechia or abnormal bleeding. After having had many medical consultations at a local hospital, no definite cause of her suffering was found. She then underwent various further investigations including a bone marrow examination at a local university hospital which did not reveal any malignant conditions. She was referred back to her home town hospital. However, she still suffered from recurrent high pyrexia, anorexia, progressive weight loss, etc. leading to many more hospital admissions. One year later, all her symptoms, including fever and back pain, seemed to get worse and she was once again admitted to the hospital. The laboratory tests at that time revealed hematocrit 27%, white blood cell count 21,600 /mL, neutrophil 95%, lymphocyte 5%, platelet 563,000 /mL, ESR 120 mm/hr., Ca 7.6 mg/dl, phosphorus 4.5 mg/dl, BUN14 mg/dl, Cr 0.9 mg/dl, Coomb's test negative, T3 179 ng/dl, TSH 1.27 mU/ml. Echocardiography showed LVEF 66 % without evidence of infective endocarditis. An abdominal ultrasound revealed a mild degree of renal parenchymal disease, normal size liver with homogeneous parenchymal disease and a normal-appearing spleen. Gastroscopy was also performed without any significant finding. Because the clinical scenario was so obscure, she was referred to Siriraj Hospital Medical School for further management on May 6, 2003. There was no significant chronic medical condition prior to this agonic episode. She neither smoked nor drank alcohol. Her adult children ran a family business within her home so she was closely looked after by her daughter and did not have any financial difficulties.

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หญิง อายุ72 ปี บ้านอยู่อำเภอนาหมื่น จังหวัดน่าน ได้รับการส่งตัวเพื่อมารับการรักษาต่อที่โรงพยาบาลศิริราชด้วยปัญหาไข้และปวดหลังมา 2 ปี อาการเริ่มด้วยอ่อนเพลีย ไข้เป็นๆ หายๆ หนาวสั่นปวดเมื่อยตามตัว เป็นมากเวลากลางคืนจนทำให้คุณยายนอนไม่หลับ ส่วนอาการปวดหลังเป็นมากตลอดทั้งกลางวันและกลางคืน พร้อมกับอาการเบื่ออาหาร ไม่พบอาการไอ จุดจ้ำเลือดตามตัว หลังจากได้รับการสืบค้นที่โรงพยาบาลใกล้บ้านหลายครั้งไม่พบสาเหตุที่ชัดเจน ยังได้รับการสืบค้นเพิ่มเติมหลายอย่างรวมทั้งการตรวจไขกระดูกที่โรงพยาบาลระดับมหาวิทยาลัยใกล้บ้าน ไม่พบสาเหตุร้ายแรงใดๆ หลังจากกลับมาพักที่บ้านก็ยังมีไข้สูงเป็นๆ หายๆ เบื่ออาหาร น้ำหนักลด ทำให้ต้องเข้ารับการรักษาในโรงพยาบาลหลายครั้ง 1 ปีต่อมา อาการต่างๆ เช่นไข้และปวดหลังเป็นมากขึ้นเรื่อยๆ การตรวจทางห้องปฏิบัติการก่อนย้ายมาที่โรงพยาบาลศิริราช พบค่า hematocrit ร้อยละ 27 จำนวนเม็ดเลือดขาว 21,600 ตัวต่อมิลลิลิตร neutrophil ร้อยละ 95 lymphocyte ร้อยละ 5 เกร็ดเลือด 563,000 ต่อมิลลิลิตร ESR 120 มิลลิเมตรต่อชั่วโมง แคลเซี่ยม 7.6 มิลลิกรัมต่อเดซิลิตร ฟอสฟอรัส 4.5 มิลลิกรัมต่อเดซิลิตร BUN 14 มิลลิกรัมต่อเดซิลิตร creatinine 0.9 มิลลิกรัมต่อเดซิลิตร การตรวจCoomb ให้ผลลบ ระดับ tri-iodothyronine 179 นาโนกรัมต่อเดซิลิตร thyroid-stimulating hormone 1.27 มิลลิยูนิตต่อมิลลิลิตร ผลการตรวจ echocardiography พบค่า LVEF ร้อยละ 66 โดยไม่พบลักษณะของการติดเชื้อที่ลิ้นหัวใจแต่อย่างใด การตรวจช่องท้องด้วยคลื่นเสียงพบความผิดปกติของเนื้อไตเล็กน้อย ตับขนาดปกติ แต่มีความผิดปกติของเนื้อตับแบบ homogeneous ม้ามปกติ การส่องตรวจกระเพาะอาหารก็ปกติ โดยสรุปการตรวจไม่พบพยาธิสภาพใดๆ ที่จำเพาะ จึงได้รับการส่งตัวมารับการรักษาในโรงพยาบาลศิริราชเมื่อวันที่ 6 พฤษภาคม พ.ศ. 2546 ผู้ป่วยไม่มีความเจ็บป่วยใดๆ ชัดเจนก่อนหน้าอาการไข้เหล่านี้ ผู้ป่วยไม่สูบบุหรี่ ไม่ดื่มสุรา บุตรของผู้ป่วยประกอบธุรกิจครัวเรือนภายในบ้าน ผู้ป่วยจึงได้รับการดูแลจากลูกสาวอย่างใกล้ชิด โดยไม่มีปัญหาทางเศรษฐฐานะแต่อย่างใด

INTRODUCTION

On physical examination, body temperature was 38.7°C, pulse 96 beats/mininute, respiratory rate 20/minute and blood pressure 100/60 mmHg.

General appearance :good consciousness, oriented, hyposthenic built, moderately pale, no jaundice, no cyanosis, no edema both legs, generalized muscle wasting without fasciculation, no clubbing of finger, no subcutaneous nodule

EENT : pale optic disc with cupping, dull macular reflex, chorioretinal scar in both eyes, pharynx & tonsils not injected, no oral ulcer

Neck : thyroid not enlarged, no cervical lymphadenopathy

CVS : JVP 3 cm. PMI at 5th intercostal space midclavicular line, no heaving or thrill, normal S1, S2, no murmur

RS : trachea in midline, symmetrical chest expansion, resonant note on percussion both lungs, normal breath sound, coarse crepitation both lungs, equal vocal resonance

Abdomen : generalized soft abdomen, no abnormal bulging, no hepatosplenomegaly, no shifting dullness, normal bowel sound

PR : normal sphincter tone, no rectal shelf

Nervous system : looked dull, apathetic, good attention, no disorganized thinking, coherent speech without dysarthria

tone - normal all extremities

muscle - generalized wasting, no fasciculation

motor power - grade IV+ all extremities, no focal neurological weakness

deep tendon reflex all 2+, Babinski sign_ absent both sides

normal finger to nose test - both arms

gait - poor standing balance

Initial laboratory investigations revealed the following :

CBC : Hb 9.0 g/dl, WBC 19,800 /μL, neutrophil 85.9%, lymphocyte 10.3%, eosinophil 1.2%, platelet 306,000 /μL

Urine exam: pH 6.0, sp.gr. 1.020, alb 1+, sugar neg, acetone 2+, bilirubin 1+, WBC 0-2/HP, RBC 0, bacteria rare, no cast, BUN 12 mg/dl, Cr 0.5 mg/dl, uric acid 5.4 mg/dl, total bilirubin 0.5 mg/dl, direct bilirubin 0.2 mg/dl, SGOT 27 U/L, SGPT 17 U/L, alkaline phosphatase 106 U/L, Na 134 mmol/L, K 4.0 mmol/L, Chloride 98 mmol/L, bicarbonate 22 mmol/L.

.Problem list

1. Chronic fever for 2-3 years
2. Chronic back pain
3. Anemia
4. Anorexia and weight loss

The patient was initially referred to the orthopaedic department of Siriraj Hospital under the supervision of Dr. Chatuporn Chotigavanich.

Dr. Chatuporn Chotigavanich's discussion :

Generally, back pain could be come from trauma, infection, tumor, degeneration, metabolic bone disease and seronegative spondyloarthropathies. Musculoskeletal causes and non-musculoskeletal causes should be differentiated by history and physical examination. In this case, three differential diagnoses involved chronic infection such as tuberculosis, malignancy such as multiple myeloma or metastatic spinal lesion and metabolic bone disease such as osteoporosis with compression fracture.

For tuberculosis, it is estimated that 10-15 percent of tuberculosis is extrapulmonary and 10 percent of extrapulmonary tuberculosis is skeletal in origin[1]. Almost half of the patients with skeletal tuberculosis have spinal involvement especially at the thoracolumbar region; the hip and knee joints are the next most frequently affected organs. Slowly progressive constitutional symptoms are predominant in the early stage of the disease, including weakness, malaise, night sweats, fever and weight loss. Mycobacterium tuberculosis is the most common[2]. Ten to 78 percent of the patients could have neurological deficit[3]. Laboratory studies suggest chronic disease such as anemia, hypoproteinemia, and mid ESR elevation. Skin testing may be helpful but is not diagnostic. Roentgenographic findings include periodical, anterior and central involvement. Bone scan is unreliable. MRI of spine may be helpful. The most definite and rapid identification of the pathologic process relies on spinal biopsy.

Multiple myeloma is the most common primary bone malignancy with incidence of 2.5 per 10,000 population[4]. Patients often present most with pain and spontaneous vertebral fractures with osteopenia on plain radiograph. The diagnosis is supported by a serum immunoelectrophoresis. In 20percent of cases, urine protein electrophoresis may be the only abnormal finding[4].

Metastatic spinal lesion is also an important differential diagnosis of progressive spinal pain and/or vertebral body collapse. Spinal cord compression occurs in 20 percent of patients with spinal metastases and in 5percent of patients who die from cancer each year[5]. Tumors that commonly metastases to the spine include lung, breast, kidney and gastrointestinal tract tumors. Metastasis from thyroid cancer is now less common as a result of early diagnosis and successful treatment of primary thyroid carcinoma. If the primary cancer site is not identified by history, physical examination, screening laboratory studies, chest radiograph and CT scan of trunk, then spinal biopsy is indicated.

The evaluation of a patient in whom osteoporosis is suspected should include a thorough medical history, imaging and laboratory studies and possibly bone histomorphometry. Osteoporotic fractures usually involve wedge compression fracture of thoracic and lumbar spine, intertrochanteric fractures and fractures of the distal end of the radius. The evaluation of bone mass[6] can be done by dual energy x-ray absorptiometry, quantitative computed tomography, single-beam densitometry and ultrasound bone attenuation, etc.

Precise determination of osteoporotic fracture when confronting a vertebral deformation on standard radiographic finding can be difficult due to lack of a universally accepted definition of fracture. Laboratory studies are used to exclude other diseases that can also cause osteoporosis or osteopenia i.e. infection and tumor. Abnormalities in laboratory blood screening are found in 2 percent of patients who have osteopenia. One half of them related to multiple myeloma. If such an abnormality is suspected, a bone biopsy or bone marrow aspiration is recommended.

Generally, acute painful osteoporotic vertebral compression fractures are treated nonsurgically with bed rest, analgesic medications, bracing, physi-

cal therapy, anti osteoporotic drugs such as vitamin D, calcitonin and bisphosphanates. If the patient's condition does not improve, surgical treatment should be further considered. Vertebroplasty[7], a minimally invasive treatment of osteoporotic vertebral compression fracture, is a procedure done by percutaneous injection of polymethylmethacrylate (PMMA) into a fractured vertebral body. Kyphoplasty[7,8], a newer minimally invasive technique, is a combination of vertebroplasty and balloon angioplasty which could have potential advantages including lower risk of cement extravasation and better restoration of vertebral body height. Standard open surgical treatment such as posterior decompression with instrumentation or anterior decompression with instrumentation can be performed in only selected patients.

In this case, her spinal balance in both sagittal and coronal plane were fine but her spinal rhythm was extremely protective and hesitative. Some tenderness along thoracic and lumbar vertebrae, especially the upper lumbar, was found. The x-ray of the whole spine, both AP and lateral views, were acceptable in both sagittal and coronal alignment even though some compression fracture of lower thoracic and upper lumbar vertebrae were found. The MRI of thoracic and lumbar spine revealed degenerative changes of the spine and collapse of T 7,9,11,12 vertebral bodies without abnormal SI on enhancement. The L1 vertebral showed abnormal hypo-signal on T1W and abnormal heterogeneous signal on T2W enhancement. However, bone biopsy should give a final diagnosis in this case.

Dr. Prasert Assantachai's discussion :

A spinal biopsy was done, and while waiting for the results, the orthopaedic team consulted with the geriatric team to discuss what other medical conditions could be causing the woman's symptoms. A review of the body temperature chart showed sustained high grade fever since admission. A definition of "fever of unknown origin" (FUO) was originally made by Petersdorf & Beeson in 1961 as having a body temperature higher than 38.3 °C on several occasions that lasts more than 3 weeks and has an uncertain diagnosis after 1 week of study in the hospital[9]. There is no doubt that this patient fell into this category. A newer fever classification system divided fever of unknown origin into classic, nosocomial, neutropenic and HIV- associated types to facilitate the clinical approach. However, when approaching FUO cases in the elderly, the clinical picture can be further complicated by the unique features of older patients, described by the mnemonic "R-A-M-P-S" : "R" represents reduced body reserve, "A" represents atypical presentation, "M" represents multiple pathology, "P" represents polypharmacy and "S" denotes social adversity[10]. Changes occur as part of the aging process that lead reduced reserves of the immunological system. Some common abnormal conditions that are related to reduced immune system function encountered among the older patients are infection, cancer and autoimmune disorders as shown in Table 1[11].

Table 1. Physiologic aging changes and their related clinical conditions.

Physiologic changes	Clinical correlation
Decreased cell-mediated immunity	Increased tuberculosis, herpes zoster, etc[12]
Increased autoimmunity	Increased rheumatoid arthritis,[13] thyroiditis,[14] temporal arteritis,[15] bullous pemphigoid[16]
Decline in antibody titers to specific foreign antigens	Impaired both primary and secondary immune response to vaccination[17]
Immunosenescence	Atypical presentation of infection[18]
Decline in delayed type skin hypersensitivity	Associations between anergy and mortality[19]

Table 2. Final diagnosis in older patients with fever of unknown origin compared with the diagnosis in younger patients studied in the same period.

Diagnosis	Older patients	Younger patients
Infection	25%	21%
Collagen vascular disease	31%	17%
Tumor	12%	5%
Drug-related fever	6%	1%
Factitious fever	0%	4%
Miscellaneous	10%	15%
No diagnosis	12%	29%

Table 3. Final diagnosis of fever of unknown origin among the elderly from 3 different studies.

Diagnoses	Esposito 1978[22]	Barrier 1982[23]	Knockaert 1993[21]
Infection	36.9%	41.3%	25%
Tumour	23.4%	13%	12%
Collagen vascular disease	25.2%	30.3%	31%
Miscellaneous	7.0%	2.1%	10%
No diagnosis	5.4%	13%	12%

As far as atypical presentation in the elderly is concerned, some authorities have redefined the definition of fever in the elderly as having an elevation of body temperature of at least 2°F from baseline values[20]. When comparing the causes of fever of unknown origin in the elderly with those found in the young, knowing the prevalence of each possible underlying disease group could be very helpful (Table 2)[21]. This patient has been sufferings from an unknown disease process for 2-3 years and she might have died before this point if the cause was either infection or cancer. Therefore, the next most common cause would be collagen vascular diseases. Interestingly, the pattern of causes of fever of unknown origin in the elderly have also changed over time as studies have shown (Table 3). Therefore, at this stage, collagen vascular diseases was on the top of the list proposed by our team.

Meanwhile, upon the advice of pulmonary specialists, sputum was examined for acid fast bacilli for 3 consecutive days. All tests implicating pulmonary tuberculosis were negative. The infectious team was notified of these tests results and the differential diagnoses were either autoimmune disease or malignancy. It was suggested to discontinue use of the current antibiotics and wait for the bone marrow biopsy results. Because the patient also suffered from anemia, hematologic consultation was also sought.

Dr. Theera Ruchutrakool' s, (hematologist), discussion:

From my point of view as a hematologist, I would like to summarize the problems in this elderly woman as anemia, back pain and hyperglobulinemia. I will start with anemia as the key feature for discussion and discuss back pain and hyperglobulinemia as associated findings.

Normal hemoglobin levels of women and men are 11.7-15.7 and 13.3 -17.7 g/dl respectively. Hemoglobin of the elderly is usually 1-2 g/dl lower than that of youth[24]. Mild anemia can be found approximately 25percent of ambulatory and healthy elderly and specific causes of anemia usually cannot

be found[25]. The exact mechanism of anemia in the elderly is not known but erythropoietin is suspected to be the cause[26]. When dealing with anemia in the elderly, physicians first have to consider whether anemia represents a true disease state and secondly how aggressively should diagnosis be pursued. Besides the common causes of anemia found in any age groups, there are also particular causes in the elderly. The hemoglobin of this woman was 9.0 g/dl, which was much lower than normal, even for an anemic elderly patient, so the specific causes of anemia had to be investigated.

In order to determine the causes of anemia, clinical features from both history and physical examination are the most helpful information. Whether the onset of anemia was classified as acute, subacute or chronic is very useful. Acute anemia that occurs within a few days could be found in cases of acute hemorrhage and some acute hemolysis cases such as hemoglobin H disease and G-6-PD deficiency anemia. Subacute or chronic anemia like this patient could be a result of either peripheral destruction or underproduction anemia. Understanding the pathophysiology of anemia will improve data collection efficacy. For example, jaundice can be found in hemolysis, both extravascular and intravascular. Hepatosplenomegaly would suggest extravascular hemolysis, myeloproliferative and lymphoproliferative disorders such as acute leukemia. Associated bleeding symptoms from thrombocytopenia can usually be found in bone marrow diseases such as acute leukemia or aplastic anemia. Although chronic anemia without abnormalities of white blood cells and platelets would suggest peripheral destruction anemia, underproduction anemia is also possible, especially iron deficiency anemia or pure red cell aplasia associated with infection or autoimmune diseases.

Finally, laboratory confirmation helps physicians make the correct diagnosis. Complete blood count is one of the most useful laboratory tests. From the CBC, anemia can be classified into three categories- hypochromic microcytic, normochromic normocytic and macrocytic anemia. For normochromic normocytic anemia, the reticulocyte count is the most helpful in distinguishing underproduction from increased destruction anemia. The low reticulocyte count in this patient implied that the anemia resulted from underproduction anemia. The most important associated symptoms in this case which pointed out the cause of anemia were back pain and hyperglobulinemia. Multiple myeloma should be considered in the elderly with anemia and back or bone pain until proven otherwise.

The possible causes of anemia in this patient are summarized in Table 4. Multiple myeloma usually presents in the fifth to sixth decade of life. Besides anemia, bone pain is the second most common complaint[27]. Other symptoms such as renal failure, fever from infection, fracture, drowsiness from hypercalcemia or uremia, polyuria and nocturia were not found in this case. Hyperglobulinemia was the only other symptom indicating multiple myeloma. However, polyclonal gammopathy from protein electrophoresis found in this patient was strongly suggestive of inflammatory process rather than multiple myeloma.

Table 4. Differential diagnosis of anemia in this patient

- multiple myeloma
- iron deficiency anemia
- anemia of chronic disease
- myelodysplastic syndrome
- anemia in the elderly

Other differential diagnosis are iron deficiency anemia, anemia of chronic disease, myelodysplastic syndrome and anemia in the elderly. Iron deficiency anemia has to be considered because she had experienced back pain for a while. Analgesics such as NSAID or steroid abuse for pain control must be considered as well. Most analgesics cause peptic ulcer and finally iron deficiency anemia. Red cell morphology and red cell indices would reveal hypochromic and microcytic red cell, which was not found in this patient. Chronic back pain may be from some inflammatory disease, so anemia of chronic disease has to be considered as well. Anemia of chronic diseases[28] occurs only in inflammatory diseases such as rheumatoid arthritis, SLE, tuberculosis etc. Anemia is usually mild (hemoglobin is not less than 7-8 g/dl)

and morphologically normochromic normocytic, but hypochromic microcytic anemia can also be found in some cases. Before the diagnosis of anemia of chronic disease is established, physicians have to exclude other causes of anemia. Myelodysplastic syndrome (MDS) should be differentiated from other causes of anemia in the elderly because MDS is not an uncommon cause of anemia in the elderly. 5q - syndrome is commonly found in the fifth to sixth decade and typically in females. A deletion of the long arm of number 5 chromosome on which many growth factor genes are located might be the cause of anemia in myelodysplastic patients. Cytogenetic studies were therefore needed for establishing the definite diagnosis.

Dr. Prasert Assantachai's discussion :

Up to this point, some progression of clinical reasoning was under way in an attempt to find the correct diagnosis in this patient. Collagen vascular disease was on top of the list while bone and bone marrow biopsy results were essential to exclude some other diseases such as myelodysplastic syndrome, multiple myeloma, tuberculosis, etc. Guller et al.[29] had proposed a clinical method for approaching FUO in the elderly as follows:

- Confirm fever by serial measures
- Thorough meticulous history, complete physical examination, CBC, ESR, liver function test, urine exam, multiple hemoculture, midstream urine culture, thyroid-stimulating hormone
- Consider HIV, EBV, CMV & ANA in specific cases
- Discontinue all nonessential drugs
- Echocardiography
- Search for tuberculosis
- Computed tomography of abdomen & chest
- Consider temporal artery biopsy, if ESR > 40
- Search for pulmonary embolism especially in bedridden case
- Gallium-67 or indium -111 labelled autologous leucocytes
- Consider liver & bone marrow biopsy
- Explorative laparotomy

The further management recommended by our geriatric team therefore included blood tests for antinuclear antibody, anti double-strand DNA, rheumatoid factor, ESR. Rheumatology consultation was sought for possible collagen vascular diseases, vascular surgery consultation for temporal artery biopsy, repeated echocardiography for possible silent infective endocarditis and sputum exam for modified acid fast bacilli for any other atypical systemic infection e.g. nocardiosis. Sequentially, all the laboratory results came back and the only positive findings revealed postive antinuclear antibody 1: 640 titer with speckled pattern, ESR 117 mm/hour, rheumatoid factor 118 IU/ml. and superficial temporal artery biopsy showed aging and hypertensive vasculopathy. Therefore, rheumatology service was called for further management.

Dr. Surasak Nilganuwong's discussion :

I would like to thank Dr. Prasert from the Department of Preventive Medicine for consulting me on this patient, a grandma with 2 years of fever and severe back pain. My colleague and I reviewed the history, physical examination and investigation of this patient. Some aspects of her presentation had changed over time. The difference of history, physical examination and investigation will be presented here. Two years before admission, she had a history of high fever, symmetrical polyarthritis of the wrists, proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, elbows and shoulders. She also had morning stiffness for 2-3 hours. She was treated by a doctor from her provincial hospital. One and a half years before admission, she was referred to the Medical School in the northern part of Thailand for treatment. Investigations (include blood tests, radiographs and bone marrow aspiration) were done to find the etiology of fever. The results of the investigations gave no clues to support any specific diagnosis. She returned to her home and was treated with symptomatic and supportive management from her provincial hospital. During this period, she still had fever and symmetrical polyarthritis. Unfortunately, she got worse, developing additional arthritis of the knees and ankles and low back pain; she could not stand and walk. The low back pain improved when she was lying down, so she spent

more time lying down than anything else. She stayed in bed almost all day. On physical examination (by me), there was swelling, redness and tenderness of PIPs, MCPs, wrists, elbows, knees and ankles joints. With the evidence of symmetrical polyarthritis from physical examination, I would like to show the evidence of structural damage from synovitis by radiographs. Look at the radiographs of both hands, which were taken on February 19, 2002 (one and a half year ago) as the Figure 1 and Figure 2. There were narrowing joint space of PIPs, MCPs and wrists with marginal erosion of 2nd to 5th PIP joints. This was confirmed by the radiographs of both hands which were done on June 10, 2002 at her provincial hospital and on June 5, 2003 at our hospital during this admission. There was more structural damage of both hands than in previous radiographs. Radiographs of chest and lumbo-sacral spine (antero-posterior and lateral view) done on June 30, 2003 showed mild cardiomegaly with generalized interstitial fibrosis with severe osteoporosis and vertebral fractures as shown in Figure 3 and Figure 4. The etiology of low back pain was due to severe osteoporosis, vertebral fractures and inactivity. Severe osteoporosis was complicated by management with corticosteroid for a long-time at her provincial hospital. She was anemic with hematocrit 27percent; leukocytosis with WBC 19,800 /mm^3; erythrocyte sedimentation rate (ESR) 117mm/hour and rheumatoid factor 118 IU/ml (normal less than 14 IU/ml).

The problems listed were fever for 2 years, symmetrical polyarthritis for 2 years, low back pain, weight loss, anemia, leukocytosis, ESR elevation, rheumatoid factor positive and osteoporosis. According to the American Rheumatism Association, a patient is said to have rheumatoid arthritis if she or he has satisfied at least four of seven criteria[30]. This patient had six criteria (morning stiffness > 1 hour, arthritis of three or more joint areas, arthritis of hand joints, symmetrical arthritis, serum rheumatoid factors and radiographic changes) of the seven. Thus, the diagnosis of this patient was rheumatoid arthritis, low back pain and severe complications of osteoporosis from aging, chronic use of corticosteroids and inactivity. Rheumatoid arthritis is chronic polyarticular inflammatory arthritis that involves not only small joints of the hands and feet but also medium and large joints. It is associated with excessive disability, morbidity and mortality. Rheumatoid arthritis is a complex inflammatory and autoimmune disease with systemic involvement and systemic symptoms.

I would like to introduce the term "Elderly-onset of rheumatoid arthritis (EORA)". Since the first description of the "rheumatic infection in the old"[31], there has been an interest in EORA as a subset of rheumatoid arthritis. Several authors have suggested that EORA, defined as rheumatoid arthritis with onset at age 60 years or over, can be distinguished from younger-onset rheumatoid arthritis (YORA)[32-39]. This patient was 70 years old, so the diagnosis was EORA. The clinical presentation of EORA and classic rheumatoid arthritis are shown in Table 5. The pattern of joint involvement in EORA is abrupt onset, polyarthritis, but some patients may be oligoarticular. Large joint involvement may dominate when compared to classic rheumatoid arthritis. Measures of disease activity, such as ESR and scores of disease activity were higher in EORA patients than in YORA. The ESR of this patient was 117 mm/hour. The very high ESR may be due to anemia and active disease. The prevalence of rheumatoid factor is decreased in elderly patients, but this patient had a very high rheumatoid factor (118 IU/ml). EORA differs slightly at presentation from younger-onset RA (YORA) by having a more equal gender distribution, a higher frequency of acute onset with systemic features. Table 6 summarizes some of the findings from major studies looking at EORA and YORA[38-41]. Duration of disease before establishing a diagnosis was longer in cases described in older reports (less 10 years) than in recent reports (less 1 year). This data indicates that the knowledge of this disorder may be improving. Studies on elderly patients with polyarthritis fulfilling the ACR criteria for rheumatoid arthritis suggest that they are a more heterogeneous group than those with YORA. The clinical manifestations of seropositive EORA, the largest subset, are similar to those of seropositive YORA, but older patients tend to have more persistently active disease and develop more radiographic damage and functional decline. This progressive course is different from that of seronegative EORA, which often leads to recovery without joint deformity[42].

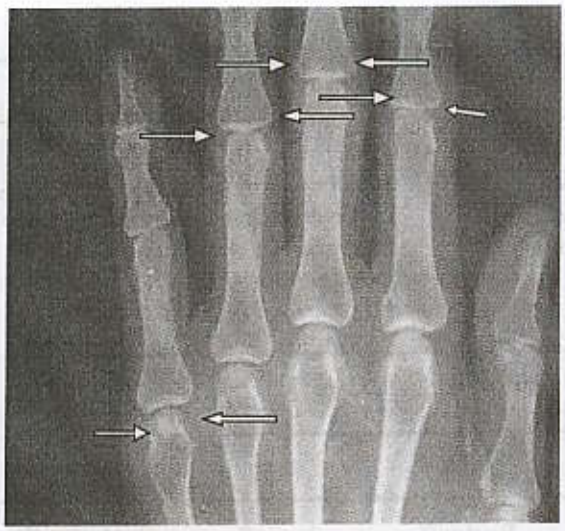

Figure 1. Radiograph of left hand on February 19, 2002 showed marginal erosion (arrow).

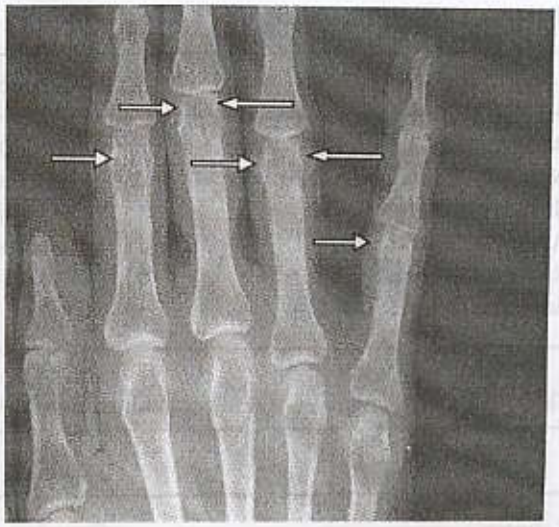

Figure 2. Radiograph of right hand on February 19, 2002 showed marginal erosion (arrow).

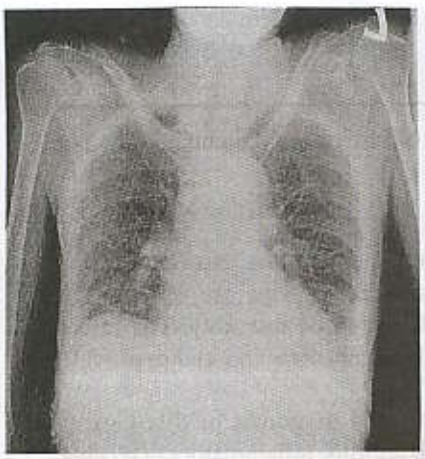

Figure 3. Radiograph of chest on April 30, 2003, there was mild cardiomegaly with generalized interstitial fibrosis.

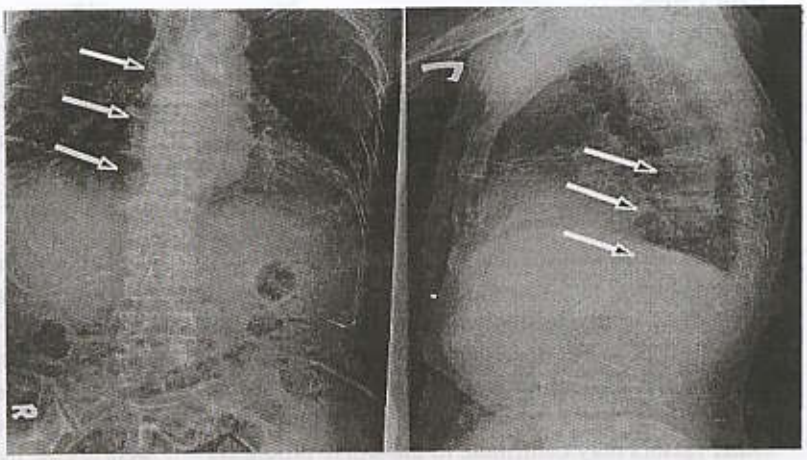

Figure 4. Radiograph of thoracic- lumbar spine on April 30, 2003, there was osteoporosis and vertebral fractures (arrow).

Table 5. Clinical presentation of RA in the elderly.

	Classic RA	EORA
Age of onset	30 - 50	> 60
Nuber of joints involved	Polyarticular	May be oligoarticular
Sites involved	Small joints	Large jt involvement may dominate
Arthritis onset	Gradual onset	Abrupt onset is more common
Rheumatoid fator	Positive	Negative-positive
Sex ratio (F:M)	3:1	1:1

Table 6. EORA versus YORA : four studies, side-by-side.

	1983	1985	1987	1991
Country	Canada[38]	Boston[39]	Japan[40]	Holland[41]
Prospective	poor	poor	poor	fair
Disease duration	<10 yr	<10 yr	ND	<1 yr
# O/Y RA	34/34	28/134	79/414	71/142
> proximal joint involvement	fair	poor	fair	fair
PMR-like	poor	fair	fair	fair
High ESR	poor	fair	fair	fair
EORA RF%	32	48	66	89
DR4+%	38	ND	44	52
Outcome	fair	fair	ND	poor

EORA : Elderly-onset RA; YORA : younger-onset RA; O/Y : Ratio of old to young patients; ND : not discussed.

Most studies show that disease activity remains high 2 to 6 years after diagnosis[41,43]. This is consistent with studies looking at RA patients regardless of age at onset; more radiologic damage, and functional decline were found in older-onset seropositive, but not seronegative RA patients[40]. Other factors may contribute to the worse prognosis in EORA patients, most importantly co-morbid disease. Most RA patients have concurrent illnesses and serious medical conditions that occur more frequently in this age group. They have less tolerance to systemic inflammation, joint destruction, and especially to side effects of various drugs used in the treatment of RA[44]. Life expectancy in RA is decreased; although the exact degree of this decrease is not clear. Cause of death in most studies were from cardiovascular causes, infections and RA itself[45]. Severe disease and older age are associated independently with increased mortality. The effect of gender on mortality is not clear and studies provide conflicting results[46].

The differential diagnosis of this patient were crystal induced arthritis, inflammatory or erosive osteoarthritis and malignancy. Monosodium urate crystal or calcium pyrophosphate dehydrate crystal deposition disease in the elderly frequently presents with sudden onset, monoarthritis and intermittent attack. There was no evidence of crystals in the synovial fluid. A minority of patients with polyarticular hand osteoarthritis have recurrent inflammation of the interphalangeal and first carpometacarpal joints[47-48]. The radiographic

findings of joints showed no evidence of osteoarthritis. However, malignancy-associated arthritis usually occurs later in life. Dr.Teera (the hematologist) explained that the CBC and bone marrow aspiration ruled out hematologic malignancy. The criteria of other syndromes that may be indistinguishable from EORA, polymyalgia rheumatica and the syndrome of remitting seronegative symmetrical synovitis with pitting edema were not met.

Management of EORA is not different from that of rheumatoid arthritis. In recent years, rheumatoid arthritis (RA) has become much more manageable. Patients now have the prospect of having their symptoms suppressed and their synovitis toned down by new medications with relatively few side effects[49]. Education, pain control, a balance of rest and exercise, temperature modalities, and drug therapy all can be instituted. It is clear that a program to restore and subsequently preserve (partial) independence may be very complex and will need the effort of the whole management team, including a rheumatologist, an orthopedic surgeon, a physical therapist, an occupational therapist, a pharmacologist, a nurse and a social worker.

I would like to remind you that this patient was referred to our hospital for diagnosis and proper management. She was treated with symptomatic and supportive treatment and corticosteroids from the provincial hospital. I suggested treating her with education, proper rest and exercise, and suppressing inflammation with NSAID and chloroquine. I did not recommend the use of corticosteroids because I was afraid of long-term adverse effects, especially severe osteoporosis. In my experience, the symptoms and signs of rheumatoid arthritis will improve 1-3 months after the proper management. Thank you very much for your attention.

Final result and diagnosis

- Spinal needle biopsy of L1 : abnormal marrow, slight hypercellularity due to mild to moderate plasmacytosis; no homogeneous nodules of plasma cells; normal number of myeloids and megakaryocytes; relative decrease in erythroids; scattered siderophages with focal marrow injury effect; negative for metastatic tumor and granuloma. Paraffin immunoperoxidase demonstrates scattered polyclonal plasma cells by IgG, IgA, IgM, kappa and lambda light chains. No monotypic aggregate of plasma cells is detected. Therefore, no definite evidence of multiple myeloma is detected histologically and immunophenotypically.
- Bone marrow biopsy : absence of granulomas or malignancy
- All hemocultures were no growth
- Diagnosis of rheumatoid arthritis was made. The patient responded satisfactorily to NSAID and chloroquine was prescribed as home treatment.

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