Acute Lupus Hemophagocytic Syndrome : Report of a Case and Review of the Literature

PIROON MOOTSIKAPUN, MD*, CHITTIMA SIRIJERACHAI, MD*,
KANCHANA CHANSUNG, MD*, RATANAVADEE NANAGARA, MD*

Abstract

The authors reported a case of systemic lupus erythematosus (SLE) with an unusual presentation. The patient presented with acute febrile illness along with progressive pancytopenia related to increasing hemophagocytic activity of histiocytes in the bone marrow. Concomitant polyarthritis, myositis, nephritis, high titer of antinuclear factor (1 : 2,560) and positive test for anti-DNA antibody made him fit the diagnostic criteria of SLE. No definite evidence of associated infections was confirmed by bacteriologic, serologic and viral studies. He did not respond to empiric antibiotic therapy but dramatically responded to corticosteroid treatment. Therefore, diagnosis of acute lupus hemophagocytic syndrome was made. The clinical presentation, laboratory diagnosis, and management of the patient are discussed and the literature was reviewed and presented.

Key word : Acute Lupus Hemophagocytic Syndrome, Hemophagocytic Syndrome, Systemic Lupus Erythematosus

MOOTSIKAPUN P, SIRIJERACHAI C,
CHANSUNG K, NANAGARA R
J Med Assoc Thai 2004; 87: 333-339

Hematologic abnormalities are usually found in systemic lupus erythematosus (SLE). Among these, anemia is the most common followed by leukopenia and thrombocytopenia. Concerning leukopenia, it was reported in one-fifth among Thai SLE patients and is usually mild to moderate in severity[1,2]. Peripheral destruction due to antilymphocyte and antigranulocyte antibodies is the convincing pathogenesis[3]. However, hematologic abnormalities caused by bone marrow suppression or destruction in SLE have been documented[4]. Reactive hemophagocytic histiocytosis is one of the conceivable mechanisms[5].

* Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

The term acute lupus hemophagocytic syndrome was first described by Wong et al[6] in 1991. They reported six cases of SLE who initially presented with acute onset of severe pancytopenia related to reactive hemophagocytosis without any evidence of bacterial or viral infections and it responded dramatically to corticosteroid treatment. Although prior to 1991, hemophagocytic syndrome associated with SLE had been mentioned[7] it was unlike those of Wong et al and they occurred simultaneously with viral infections.

The authors demonstrated a case of SLE which presented with pancytopenia caused by reactive hemophagocytosis without associated infections. Diagnosis of acute lupus hemophagocytic syndrome had been made. The clinical course, treatment and outcome were presented.

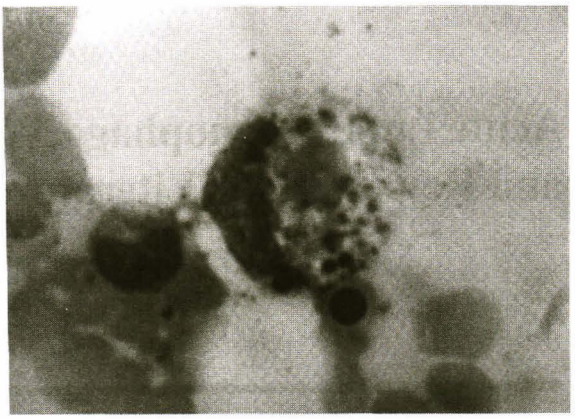

Fig. 1. Hemophagocytosis of erythrocytes in bone marrow of the lupus patient.

A CASE REPORT

A 36 year-old Thai man who was working as a government officer at Roi Et Province, presented with acute febrile illness for a week accompanying headache, severe myalgia, sore throat, and acute polyarthritis. Three months ago he had a history of recurrent polyarthritis which responded well to indomethacin therapy, and also had self-limited mucous bloody diarrhea a week prior to this illness. He looked toxic on physical examination. There was flushing of the face and eschar-like lesions over his right lateral malleolus and he had right inguinal lymphadenopathy. His complete blood count (CBC) revealed hematocrit 38 per cent, white blood cell (WBC) count 4,200/mm^3, 53 per cent polymorphonuclear cells (PMN), 17 per cent band form, 29 per cent lymphocytes, 1 per cent eosinophils, and normal platelet smear. Hemocultures, Weil-Felix and Widal agglutination test were performed. He was initially treated with oral doxycycline 400 mg/day as an outpatient.

Within 2 days after initiation of therapy, he came back with anorexia, fatigue and relapsing maculopapular rash over the trunk and he was admitted. CBC was repeated and it showed hematocrit 34 per cent, the white blood cell had count declined to 2,750/mm^3, 79 per cent PMN, 1 per cent band form, 18 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophils, and normal platelet smear. Urinalysis revealed specific gravity 1.006, albumin 2+, red blood cell (RBC) 2-4 and WBC 0-1 per high power field. There was WBC and RBC in the stool examination but no pathogenic organism was isolated. He felt better after 3-days' supportive care and intravenous doxycycline therapy, then he was discharged.

Although he had taken one week of doxycycline, he still had fever, rash, fatigue, anorexia, weight loss and myalgia. He developed pancytopenia as follows; hematocrit 30 per cent, WBC 1,500/mm^3 with 72 per cent PMN, 6 per cent band form, 22 per cent lymphocytes and platelet count 100,000/mm^3. Bone marrow aspiration was done and it revealed normal cellularity, increasing mature histiocytes with hemophagocytic activity as demonstrated in the Fig. 1. There was no definite evidence of infections confirmed by bacterial cultures, serology (Weil Felix and Widal agglutination test, melioid titer) and viral study (including HIV, Influenzae, Parainfluenzae 1 and 3, Respiratory syncytial virus, Adenovirus and Herpes simplex). There was marked elevation of muscle enzymes: serum aspartate aminotransferases (SGOT) 542 U/L (normal 12-32 U/L), creatine phosphokinase (CPK) 2,367 U/L (normal 25-200 U/L), profuse proteinuria (10 g/day), high titer of antinuclear antibody (ANA) titer (1 : 2,560) and positive test for anti-DNA antibody (1:20). Serum complements were low: C3 < 20 mg/dl (60-140 mg/dl), C4 < 5 mg/dl (17-40 mg/dl) and CH_{50} 10 U/ml (16-38 U/ml).

Although he fitted the diagnostic criteria of SLE, associated infection could not be thoroughly excluded. So ampicillin and gentamycin were empirically given intravenously during the first week. However, he did not improve and pancytopenia was still present (hematocrit 31 per cent, WBC count 1,900/

mm^3 and platelet count 113,000/mm^3. Then prednisolone 1 mg/kg/day was started along with antibiotics. Within a few days of steroid therapy, he got worse by hospital acquired *Pseudomonas aeruginosa* pneumonia therefore prednisolone was withheld and anti-*Psuedomonas* antibiotics were started.

After a 2 week-course of antibiotics, he felt better and the fever disappeared. His hematocrit was 29 per cent, WBC count and platelets count rose to 9,500/mm^3 and 252,000/mm^3. Bone marrow aspiration revealed normal cellularity with dissolution of hemophagocytic activity of histiocytes. Proteinuria declined to 3.54 gram/day and muscle enzymes returned to normal, but serum C3 was still low (< 20 mg/dl). While he was medication-free, fever relapsed within one week with the complaint of a sore throat and a dry cough. By now pancytopenia was present again with hematocrit 31 per cent, WBC count 1,500/mm^3 with 80 per cent PMN, 20 per cent lymphocytes, and platelet count had slightly decreased. Urinalysis showed RBC 10-15/per high power field and 1+ albumin.

At this time, no associated infections were documented. A third bone marrow aspiration smear also showed increasing hemophagocytic activity of histiocytes as in the first smear. Although anti-*Pseudomonas* antibiotics were given, he became progressively worse. He had high fever, confusion and intermittent dyspnea without chest roentgenographic and arterial blood gas abnormalities. He had jaundice and abnormal liver function test as follows; cholesterol 145 mg/dl, total protein 5.2 g/dl, serum albumin 2.6 g/dl, serum globulin 2.6 g/dl, total bilirubin 2.35 mg/dl, direct bilirubin 1.63 mg/dl, serum alanine aminotransferases (SGPT) 158 U/L, SGOT 549 U/L and alkaline phosphatase 246 U/L. He also had watery diarrhea with negative stool culture. The hematocrit dropped to 26 per cent with normal reticulocyte count, WBC count was 3,500/mm^3 and platelet smear was slightly decreased. There was proteinuria of 4.8 g/day and serum creatinine of 2.6 mg/dl. Serum C3 level was lower than 20 mg/dl and ANA titer was 1 : 640. So intravenous dexamethasone 5 mg every 6 hours was then started. His clinical symptoms gradually improved within 2 weeks. Body temperature became normal. Leukopenia and thrombocytopenia were resolved but normochromic normocytic anemia was still present. Prednisolone 1 mg/kg/day was given when he was discharged.

During follow-up, prednisolone was gradually tapered. Urinalysis and hematocrit returned to normal within 2 and 4 months, respectively. He was doing well at one-year follow-up with a maintenance dose of prednisolone 5 mg/day. His final hematocrit was 40 per cent and WBC count was 9,200/mm^3 as well as normal platelet count. The follow-up bone marrow aspiration result was normal.

DISCUSSION

Hemophagocytic syndrome (HS) is a clinicopathologic entity which was first described in 1939, which referred as histiocytic medullary reticulosis (8). It is characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in bone marrow, liver, and lymph nodes(9). The hemophagocytosis findings revealed activated macrophages or histiocytes engulfing erythrocytes, leukocytes, platelets and precursor cells(10). Although hemophagocytic syndrome was initially found with malignancy(11), it is now associated with a variety of causes such as familial form(12), infection(13) as well as collagen vascular diseases(6,14-22). So hemophagocytic syndrome can be divided into two categories; infections associated and non-infections, associated HS, the first of which is more common. HS associated with autoimmune diseases is very rare. There are a few reports of HS associated with systemic lupus erythematosus, dermatomyositis, adult onset Still's disease, rheumatoid arthritis and systemic lupus erythematosus (SLE)(6, 14-22). In 1991 Wong et al(6) reported six cases of SLE initially presented with acute onset of pancytopenia due to marrow hemophagocytosis without evidence of infection. The pancytopenia responded dramatically to steroid treatment. So the term acute lupus hemophagocytic syndrome has been adopted for this condition.

Acute lupus hemophagocytic syndrome is an uncommon entity. There are a few cases reported in the literature as summarized in Table 1. In addition to high fever and pancytopenia, the presenting symptoms included chills, night sweats, weakness, fatigue, anorexia, weight loss, maiaise, gastrointestinal and/or upper respiratory tract complaints. The duration of the illness ranged from 5 days to 3 weeks. Generalized lymphadenopathy may be detected in about half of the cases. Skin lesions such as vasculitic rash, malar rash, or intermittent maculopapular rash, which hardly differentiated from viral exanthems, have been reported. Some patients had concurrent nephrotic syndrome and severe abdominal pain mimicking acute appendicitis. The presented patient had concomitant severe myositis and vasculitis-like skin lesions. Clinical presentation of acute lupus hemophagocytic syndrome

Table 1. Summary of clinical features of acute lupus hemophagocytic syndrome reported in literature.

Reference no.	Clinical features	Treatment	Outcome
7	Female, 12 years old, 1 week fever, generalized lymphadenopathy, hepatomegaly, nephrotic syndrome	Steroid	Recovered
7	Male, 58 years old, 3 week fever, left axillary adenopathy, mild hepatomegaly	Steroid	Recovered
7	Female, 26 years old, 1 week fever, facial rash, cervical lymphadenopathy	Steroid	Recovered
7	Female, 28 years old, 2 day fever and abdominal pain	Steroid	Recovered
7	Female, 46 years old, 1 week fever, vasculitic rash	Steroid	Recovered
7	Female, 64 years old, 5 day fever, vasculitic rash, hepatomegaly	Steroid	Recovered
17	Known SLE, fever, anemia, leukopenia	Steroid, IVIG, cyclophosphamide	Recovered
18	Female 42 years old, known SLE, fever, rash, lymphadenopathy, liver dysfunction	Plasma exchange, cyclosporin, steroid	Recovered
19	4 females with known SLE, pancytopenia	Steroid	3 recovered, 1 died
20	Male, 15 years old, known SLE, fever, polyarthralgia, hepatosplenomegaly, leucopenia, thrombocytopenia	Steroid, cyclosporin	Recovered
21	Female, 11 years old, known SLE, panniculitis	Steroid, IVIG	Recovered
22	Female, 11 years old, fever, bilateral salivary gland swellings, leucopenia, thrombocytopenia	Steroid, cyclosporin	Recovered

cannot be exactly differentiated from HS related to other conditions[6,13-22]. Acute hemophagocytosis might be the initial presentation of SLE or occurred during clinical course of known case of SLE. The presented patient had HS as the initial presentation and also had other manifestations, which fulfilled the criteria of SLE set by the American Rheumatism Association[23] as follows; polyarthritis, proteinuria, positive ANA and anti-DNA. The bone marrow smear showed hypercellularity and the most prominent feature was an increase in mature looking histiocytes scattered among the hemopoietic cells, many of which had phagocytized erythrocytes, platelets and granulocytes compatible with HS. Cytologically malignant cells were absent. Dyserythropoietic changes and mild plasmacytosis were seen. These pathologic findings were also found in the lymph nodes and liver of patients with HS[10].

The presented case responded rapidly to steroid therapy within 2 weeks. All of the reported patients also recovered rapidly after steroid or immunosuppressive treatment[6,17-22]. The dose of prednisolone used in the case reports of Wong et al varied between 1-2 mg/kg/day depending on the severity of the disease patients.

Interestingly, leukopenia in the presented patient together with the clinical symptoms tended to improve transiently after empiric antibiotic administration without concomitant steroid treatment. This made the authors believe that hemophagocytic activity in SLE patients might be triggered by infection and transiently improved after infection had abated; however it tended to recur within a short period of time unless SLE was appropriately treated with corticosteroid. Moreover, bacterial infections may occur in acute lupus hemophagocytic syndrome as the complication of granulocytopenia itself. In the presented case, his clinical course did not favor the possibility of infection related HS which should have worsened with steroid therapy.

Pathogenetic theory of acute lupus hemophagocytic syndrome proposed by Wong favors the role of immune complex mediated mechanism[6] according to clinical vasculitis, high ANA titer and low complement level. The deposition of circulating immune complex on the marrow hemopoietic cells makes them the innocent bystanders scavenged by the histiocytes. The other theory suggests histiocytic stimulating antibodies as activating factors of hemo-

phagocytosis. It is also postulated that increase in hemophagocytosis may result from aberrant production of certain activating cytokines[24] such as interferon-g[25], tumor necrosis factor-α[26], and interleukin-18[27], particularly in infection associated HS but the exact the mechanism remains unclear. Whatever mechanism, the end result of acute lupus hemophagocytic syndrome is intramedullary destruction of hemopoietic cells and peripheral blood cytopenia.

For patients with infection associated HS, supportive care and treatment of the underlying infection is associated with recovery in 60-70 per cent[25]. Because acute lupus hemophagocytic syndrome is rare, there is very limited data for recommendation of effective treatment. According to T lymphocyte activation theory, chemotherapy with or without cyclosporin A or antithymocyte globulin may have a role in therapy[6,13-22]. Although there are only a few reports, steroid treatment seems to be very effective in autoimmune associated hemophagocytosis[6,13-22,28-30]. Data from the literature review (Table 1) revealed good response to steroid and immunosuppressive drugs that only one case died despite a high dose of steroid treatment.

In summary, the authors report a very rare case of acute hemophagocytosis as first presentation of systemic lupus erythematosus and review the current data of this condition. When confronted with an SLE patient in whom pancytopenia occurs, the possibility of HS must always be considered. Appropriate cultures and serologic studies for viral, bacterial, fungal, and parasitic organisms should be obtained to differentiate from infection associated HS. Evidence for other active organ involvement and serologic tests for SLE should be evaluated. Any immunosuppressive drugs should be withheld if clinically feasible. Initial antibiotic coverage based on clinical finding is appropriate pending verifications by culture or special stains. Failure to recover without documented infection together with high titer of ANA may represent acute lupus hemophagocytic syndrome. The conventional dose of prednisolone is used only after the criteria for diagnosis of SLE has been met and will result in rapid improvement of this syndrome.

(Received for publication on February 18, 2001)

REFERENCES

1. Deesomchok U, Tumrasvin T. Clinical study of Thai patient with systemic lupus erythematosus. J Med Assoc Thai 1983; 66: 680.
2. Nanagara R, Nantiruj K. Clinical study of systemic lupus erythematosus in North East Thai patients. Intern Med 1989; 5: 125-31.
3. Boxer LA, Greenberg MS, Boxer GJ, Stossel TP. Autoimmune neutropenia. N Engl J Med 1975; 293: 748-53.
4. Duckam DJ, Rhyne Rl Jr, Smith FE, Williams RC Jr. Retardation of colony growth *in vitro* of bone marrow culture using sera form patients with Felty's syndrome, disseminated lupus erythematosus (SLE), rheumatoid arthritis, and other disease states. Arthritis Rheum 1975; 18: 323-33.
5. Sekigawa I, Suzuki J, Nawata M, et al. Hemophagocytosis in autoimmune disease. Clin Exp Rheumatol 2001; 19: 333-8.
6. Wong KF, Hui PK, Chan JKC, Chan YW, Ha SY. The acute lupus hemophagocytic syndrome. Ann Intern Med 1991; 144: 387-90.
7. Reiner AP, Spivak JH. Hematophagic histiocytosis: A report of 23 new patients and a review of literature. Medicine (Baltimore) 1988; 67: 369-88.
8. Scott R, Robb-Smith A. Histiocytic medullary reticulosis. Lancet 1939; 2: 194-8.
9. Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol 1991; 18: 29-33.
10. Favara B. Hemophagocytic lymphohistiocytosis: A hemophagocytic syndrome. Semin Diagn Pathol 1992; 9: 63-74.
11. Wong KF, Chan JKC. Reactive hemophagocytic syndrome-A clinicopathologic study of 40 patients in an Oriental population. Am J Med 1992; 93: 177-80.
12. Janka G. Famillial hemophagocytic lymphohistiocytosis. Eur J Pediatr 1983; 140: 221-30.
13. Fishman DN. Hamophagocytic syndrome and infection. Emerg Infect Dis 2000; 6: 601-8.
14. Onishi R, Namiuchi S. Hemophagocytic syndrome in a patient with rheumatoid arthritis. Intern Med 1994; 33: 607-11.
15. Kumakura S, Ishikura H, Munemasa S, Adachi T, Murakawa Y, Kobayashi S. Adult onset Still's disease associated hemophagocytosis. J Rheumatol 1997; 24: 1645-8.
16. Yasuda S, Tsutsumi A, Nakabayashi T, et al. Hemophagocytic syndrome in a patient with dermatomyositis. Br J Rheumatol 1998; 37: 1357-8.
17. Javier RM, Sibilia J, Offner C, Albert A, Kuntz JL. Macrophage activation syndrome in lupus. Rev Rhum Ed Fr 1993; 30: 831-5.
18. Papo T, Andre MH, Amdura Z, et al. The spectrum of reactive hemophagocytic syndrome in systemic lupus erythematosus. J Rheumatol 1999; 26: 927-30.
19. Aoki A, Hagiwara E, Ohno S, et al. Case report of systemic lupus erythematosus patient with hemophagocytic syndrome, treated with plasma exchange, with specific refence to clinical profile and serum cytokine levels. Ryumachi 2001; 41: 945-50.
20. Mori Y, Sugiyama T, Chiba R, et al. A case of systemic lupus erythematosus with hemophagocytic syndrome and cytophagic histiocytic panniculitis. Ryumachi 2001; 41: 31-6.
21. Lonceint J, Sassolas B, Lefur JM, Guillet G, Leroy JP. Panniculitis and macrophage activation syndrome in a child with lupus erythematosus. Ann Dermatol Venereol 2001; 128: 1339-42.
22. Moriguchi N, Sato W, Miyata H, Yoshioka K. Systemic erythematosus with bilateral salivary gland swelling and clouding of consciousness accompanied by hemophagocytic syndrome - a study of serial determination of serum cytokines. Rinsho Ketsueki 2002; 43: 931-6.
23. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271-7.
24. Fujiwara F, Hibi S, Imashuku S. Hypercytokinemia in hemophagocytic syndrome. Am J Pediatr Hematol 1998; 67: 205-6.
25. Ohga S, Matsuzaki A, Nishizaki M, et al. Inflammatory cytokines in virus-associated hemophagocytic syndrome: Interferon gamma as a sensitive indicator of disease activity. Am J Pediatr Hematol Oncol 1993; 15: 291-8.
26. Watanabe M, Shimamoto Y, Yamaguchi M, Inada S, Miyazaki S, Sato H. Virus-associated hemophagocytosis and elevated serum TNF-alpha with parvovirus B19-related pancytopenia in patients with hereditary spherocytosis. Clin Lab Haematol 1994; 16: 179-82.
27. Takada H, Ohga S, Mizuno Y, et al. Oversecretion of IL-18 in hemophagocytic lymphohistiocytosis. A novel marker of disease activity. Br J Haematol 1999; 106: 182-9.
28. Tsuda H, Shirono K. Successful treatment of virus-associated haemophagocytic syndrome treated with cyclosporin A: Supported by granulocyte colony-stimulating factor. Br J Haematol 1996; 93: 572-4.
29. Blanche S, Caniglia M, Girault D, Landman J, Griscelli C, Fisher A. Treatment of hemophagocytic lymphohistiocytosis with chemotherapy and bone marrow transplantation: A single-center study of 22 cases. Blood 1991; 78: 51-4.
30. Gill D, Spencer A, Cobcroft R. High-dose gammaglobulin therapy in the reactive haemophagocytic syndrome. Br J Haematol 1994; 88: 204-6.

ภาวะกินเม็ดเลือดเฉียบพลันจากโรคลูปุส

ภิรุญ มุตสิกพันธุ์, พบ, จิตติมา ศิริจีระชัย, พบ*, กาญจนา จันทร์สูง, พบ*, รัตนวดี ณ นคร, พบ**

รายงานผู้ป่วย 1 รายที่เป็นโรคลูปุสและมีอาการทางคลินิกที่พบได้น้อย ผู้ป่วยมาด้วยเรื่องไข้สูงหนาวสั่นเฉียบพลัน และมีเม็ดเลือดทุกชนิดต่ำเนื่องจากมีการเก็บกินเม็ดเลือดในไขกระดูกโดยเซลล์ฮีสติโอไซต์เพิ่มขึ้นมาก ผู้ป่วยได้รับการวินิจฉัยว่าเป็นโรคลูปุสตามเกณฑ์การวินิจฉัยคือ ข้ออักเสบหลายข้อ กล้ามเนื้ออักเสบ ไตอักเสบ มีค่าแอนตี้นิวเคลียร์แฟคเตอร์สูง (1 : 2,560) และการตรวจหาแอนตี้ดีเอ็นเอให้ผลบวก จากการตรวจหาการติดเชื้อแบคทีเรีย ไวรัสและการติดเชื้ออื่น ๆ ที่ใช้การตรวจน้ำเหลือง ไม่พบว่ามีการติดเชื้อ ผู้ป่วยอาการไม่ดีขึ้นทั้งที่ได้ยาปฏิชีวนะที่ให้ไปก่อนแต่ตอบสนองอย่างดีมากต่อการให้สเตียรอยด์ ดังนั้นจึงวินิจฉัยว่าผู้ป่วยเกิดภาวะกินเม็ดเลือดเฉียบพลันจากโรคลูปุส ได้รายงานอาการแสดงทางคลินิก ผลการตรวจทางห้องปฏิบัติการณ์ และการรักษาของผู้ป่วยรายนี้ และเสนอข้อมูลที่ได้จากการทบทวนวารสาร

คำสำคัญ : ภาวะกินเม็ดเลือดเฉียบพลันจากโรคลูปุส, ภาวะกินเม็ดเลือดเฉียบพลัน, โรคลูปุส

ภิรุญ มุตสิกพันธุ์, จิตติมา ศิริจีระชัย, กาญจนา จันทร์สูง, รัตนวดี ณ นคร
จดหมายเหตุทางแพทย์ ฯ 2547; 87: 333–339

* ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, ขอนแก่น 40002