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Causes of death in autopsied cases of leukemia.

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Thirty autopsied cases of leukemia from 1978 to 1987 were reviewed. Majority of the cases were acute leukemia with ages ranging from 32 days to 78 years. The most common cause of death was infection followed by hemorrhage, organ failure and miscellaneous causes respectively. Infection was mainly caused by gram negative bacilli with a striking number of fungal-infection. The most common site of hemorrhage was intracranial. Causes of hemorrhage were thrombocytopenia and hyperleukocytosis. The causes of organ failure were leukemic infiltration and acute tumor lysis syndrome. The most common sites of extramedullary infiltration were spleen, liver and lymph node.

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มนชนก สุวิชาญวรสิน, เสาวณีย์ เข็นฤดี. สาเหตุตายในผู้ป่วยมะเร็งเม็ดเลือดขาวที่ได้รับการตรวจศพ. จุฬาลงกรณ์เวชสาร 2532 สิงหาคม; 33(8) : 607-614

การรักษามะเร็งเม็ดเลือดขาวด้วยเคมีบำบัดในปัจจุบัน เป็นผลให้สาเหตุตายส่วนใหญ่เกี่ยวข้องกับผลแทรกซ้อนของโรคเอง และผลของการรักษา จากการตรวจผู้ป่วยมะเร็งเม็ดเลือดขาว 30 ราย ตั้งแต่ปี 2521 ถึง 2530 พบว่าผู้ป่วยส่วนใหญ่เป็นมะเร็งเม็ดเลือดขาวชนิดเฉียบพลัน ผู้ป่วยมีอายุตั้งแต่ 32 วัน ถึง 78 ปี สาเหตุตายที่พบมากที่สุด คือ การติดเชื้อ รองลงมาได้แก่ การตกเลือด ระบบการทำงานของอวัยวะล้มเหลวและอื่น ๆ ตามลำดับ แบคทีเรีย گرمลบเป็นสาเหตุส่วนใหญ่ของการติดเชื้อในกลุ่มที่เกิดจากแบคทีเรีย และการติดเชื้อราที่พบได้มากเช่นกัน การตกเลือดพบบ่อยที่สุดในช่องกะโหลก สาเหตุของการตกเลือด คือ ภาวะเกร็ดเลือดต่ำ และภาวะเม็ดเลือดขาวสูง สาเหตุของระบบการทำงานของอวัยวะล้มเหลวเกิดจากการแทรกซึมของเซลล์มะเร็งในอวัยวะต่าง ๆ และกลุ่มอาการที่เกิดจากการสลายตัวของเซลล์มะเร็งอย่างเฉียบพลัน อวัยวะที่พบเซลล์มะเร็งแทรกซึมมากที่สุดคนนอกจากไขกระดูก ได้แก่ ม้าม ตับ และต่อมน้ำเหลือง

Leukemia is a well known disease which is found in every age group. The patterns of age distribution vary according to cell type⁽¹⁾ At the present, there is much increase in rate of remission as well as clinical improvement following modern chemotherapy and supportive cares.⁽²⁾ However, death can occur even during complete remission.⁽³⁾ Failure of treatment following initial remission induction is found as high as 43 per cent in acute myelogenous leukemia.⁽⁴⁾ Causes of death are mainly related to effects of leukemia itself as well as to therapeutic complications.^(5,6)

This article reports causes of death in autopsied causes of leukemia from 1978 to 1987 at the Department of Pathology, Faculty of Medicine, Chulalongkorn University. In addition, frequencies of leukemia infiltration in various organs are also analysed.

Material and Method

A total of 30 autopsy reports of leukemia from 1978 to 1987 were reviewed. Main causes of death were determined with possible detail in some categories. Extent of leukemic cells infiltration was also described.

Results

Sixteen cases were acute-non-lymphoblastic leukemia (ANLL), ten acute lymphoblastic leukemia (ALL), three chronic lymphocytic leukemia (CLL) and one was chronic myelocytic leukemia (CML). Fourteen patients were men and sixteen were women. The ages ranged from 32 days to 78 years. Peak age incidences of ANLL and ALL were in the third and first decades respectively (Figure 1).

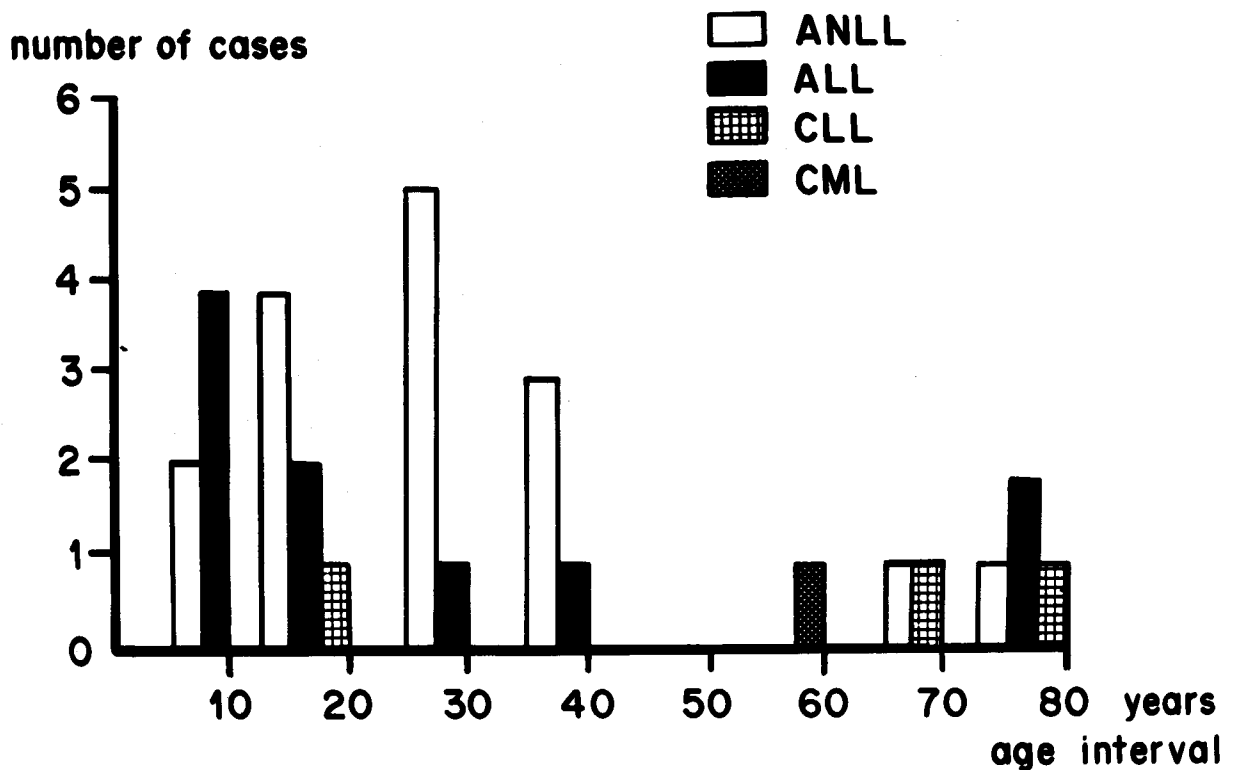


Figure 1. Age distribution

Infection was the most common cause of death involving 15 cases following by hemorrhage, organ failure and miscellaneous causes coming next in frequency (Table 1). There were ten cases of bacterial, four of fungal and one of protozoal infections (Table 2). Infected organs were mainly lung or gastrointestinal tract. Gram negative bacilli were the most frequent causative organisms. The definitive organisms obtained were 2 cases of *Pseudomonas aeruginosa*, on each of *Shigella* gr.B,

Escherichia coli, and mixed *Proteus mirabilis* plus *Enterobacter* species. There were two cases of *Mycobacterium tuberculosis* and one of gram positive diplococci. Sepsis after perforated necrotizing enteritis without bacteriologic study in two cases were included in this group. Fungal infection was found in 4 cases (26.7%). Two cases were from *Aspergillus* species (Figure 2) and one each from *Candida* and *Phycomycete* species. The protozoal case was *Pneumocystis carinii* (Figure 3).

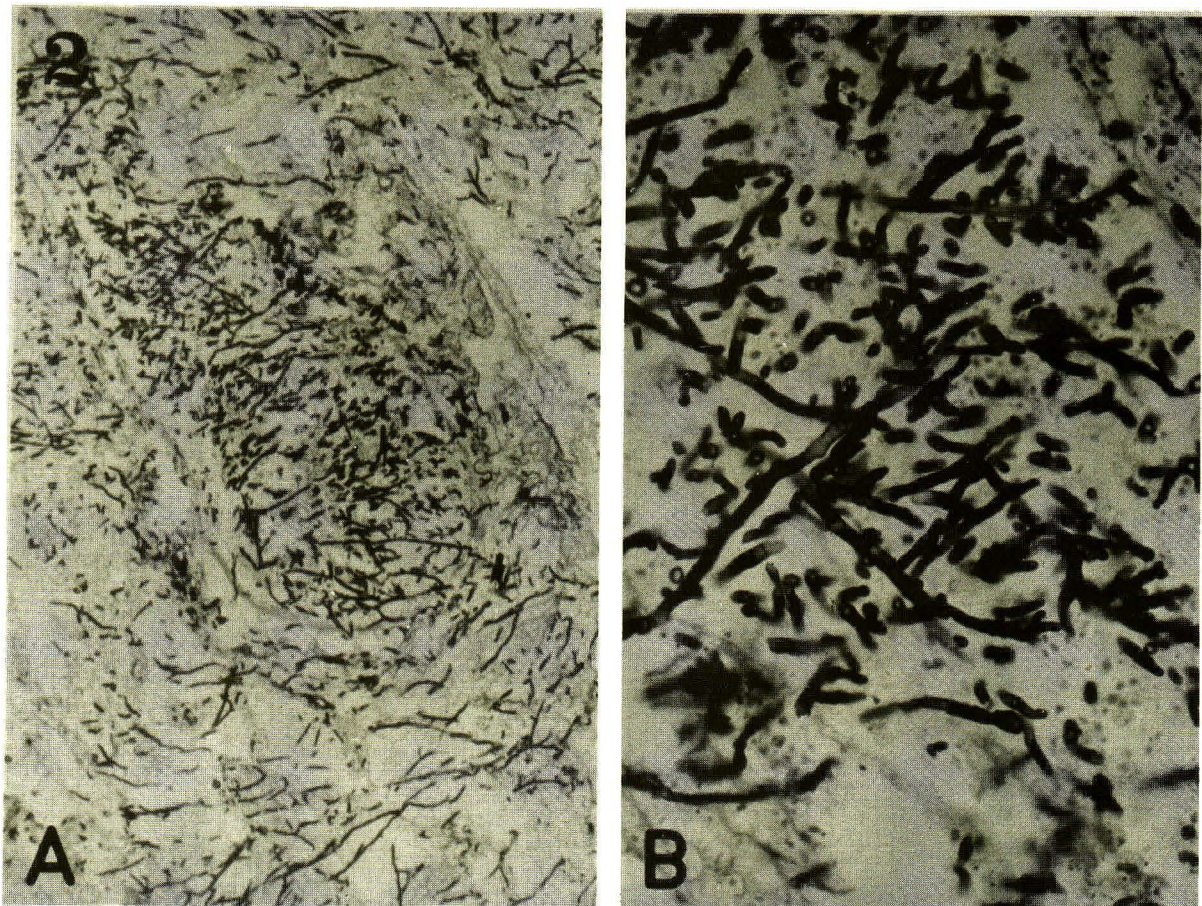


Figure 2. A. Illustration of lung shows aspergillosis in vascular lumen forming thrombus, GMS $\times 100$
B. High power view of *Aspergillus* shows branching septate hyphae, GMS $\times 400$

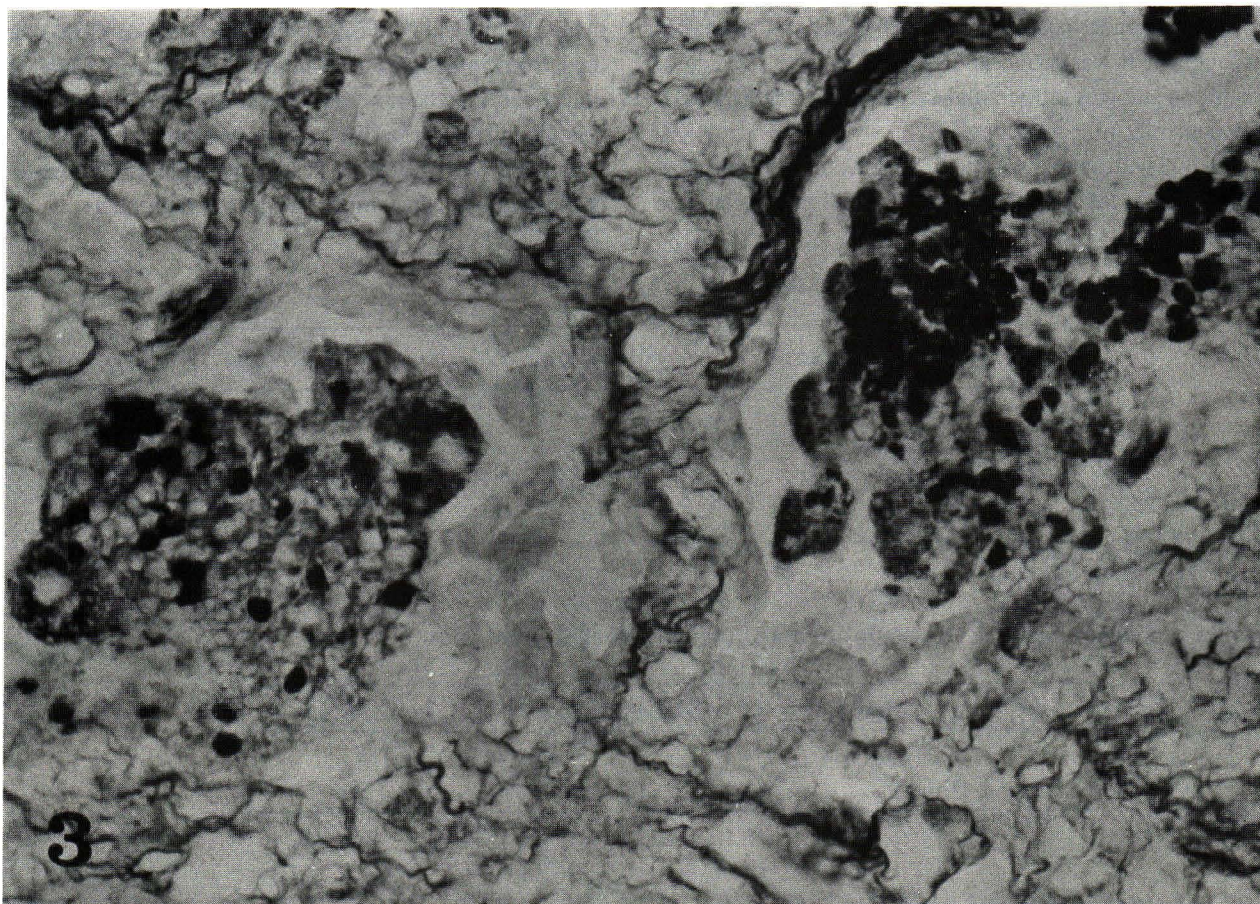


Figure 3. Photomicrograph of lung demonstrates intra-alveolar exudate containing round and oval bodies of *Pneumocystis carinii*, GMS $\times 400$

Table 1. Main causes of death in leukemia.

Causes of death	No. of cases	%
Infection	15	50
Hemorrhage	10	33.3
Organ failure	3	10
Miscellaneous	2	6.7
Total	30	100

Table 2. Major organisms in infection.

Organisms	No.	%
Bacteria	10	66.7
Fungus	4	26.7
Protozoa	1	6.6
Total	15	100

Hemorrhage as a cause of death was second in frequency. It was found in 10 cases (33.3%). The most common site was intracranial in 5, followed by gastrointestinal tract in 3 and lung in 2.

Neutropenia was highly related to infection.^(7,8) As shown in table 3, absolute neutrophil count was less

than 500/mm³ in 10 cases or 66.7 per cent of those who died from infection but granulocytopenia was found in only 2 out of 10 hemorrhage cases. Duration of admission was also different between these two groups (Table 4). In the first week, cause of death was mainly from hemorrhage but after that infection was predominant.

Table 3. Relation between WBC and causes of death.

Neutrophil count/mm. ³	Infection	Hemorrhage
< 500	2	10
500-1000	0	1
> 1000	4	2
unknown	4	2

Table 4. Relation between causes of death and duration of admission.

Duration of admission	infection	hemorrhage
< 7 days	4	7
> 7 days	11	3

There were three cases of organ failure; two of them died from leukemic cells infiltration in multiple organs and liver. The other one was a 28 year-old woman with ANLL who died from extensive necrosis of brain, bone marrow and spleen after 5 days of chemotherapy. Two patients in the miscellaneous group died from gastric aspiration and desquamative interstitial pneumonia of undetermine nature.

Bone marrow involvement was noted in 25 cases. Other various organs were involved in 23 cases out of 25. The percentages of extramedullary infiltration in each type of leukemia were as follow:— 86.2 per cent of ANLL, 80 per cent of ALL, 66.7 per cent of CLL and no infiltration in CML. Site of involvement in order of frequency was spleen, 23 cases; liver, 21; lymph node, 15; kidney, 11; adrenal gland, 9; lung, 7; brain, 6; gastrointestinal tract and heart 5 cases each; uterus, 3; skin, 2; dura mater, thyroid gland, skeletal muscle, synovial tissue and oral mucosa 1 case each. All five cases with hypoplastic marrows died from infections, two from perforated segmental necrotizing enteritis with peritonitis and one each from bacterial esophagitis, systemic candidiasis and pulmonary aspergillosis.

Discussion

Infection is the most common cause of death in patients with leukemia. In this series, the main contri-

buting factor to bacterial infection is neutropenia, often less than 500/mm³. The other related factor concerns the duration of hospitalization. More than a week of admission results in frequent nosocomial infection as a cause of death. Previous studies have shown increased bowel colonization of bacterial pathogen and changing pattern of normal flora in leukemia patients after a week of admission.^(9,10) Moreover, it has been revealed that multiple immunologic defects may occur in leukemia such as decreased neutrophil, lymphocyte, monocyte and complement activities.⁽⁸⁾ Cytotoxic drugs further enhance these effects. Thus infection is increased during period of chemotherapy. Eighty percents of our patients who died from infection had received chemotherapy during hospitalization.

Fungal infection becomes an important problem particularly if the patients receive chemotherapy and prolonged period of antibiotics administration. Clinical diagnosis is often delayed. Active tuberculosis should be suspected especially in endemic area. Necrotizing enteritis is another difficult problem. Severe form of the disease which leads to bowel perforation should be treated by surgery but decision is usually delayed in patients with pancytopenia similar to our cases.

Hemorrhage in our patients partly resulted from marked decrease in platelet count. The platelet count was done in six cases of this group and three of them were

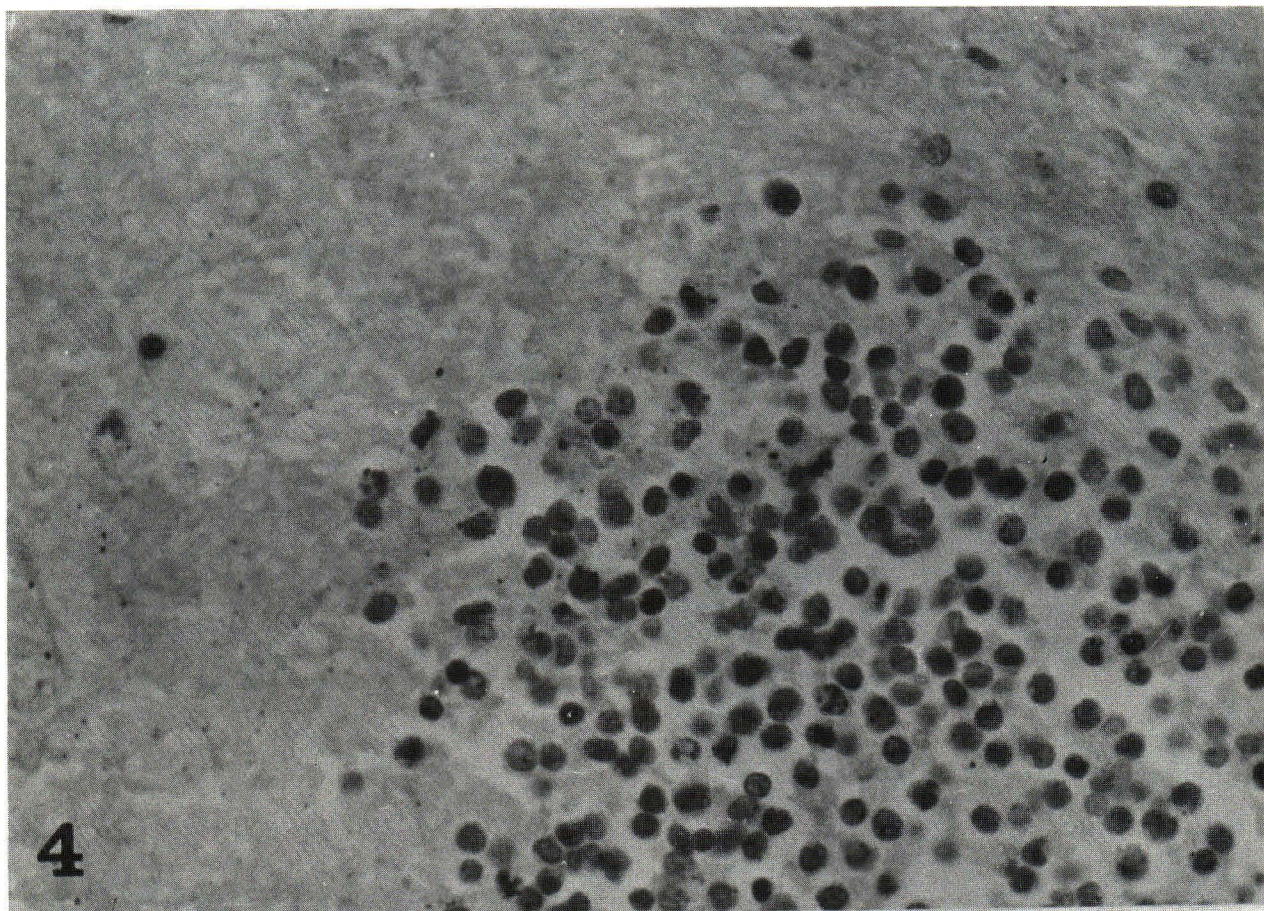


Figure 4. Leukemic cells with brain infiltration are shown, H & E \times 400

20,000/mm³ or below. Therefore true thrombocytopenia may not be the only reason for hemorrhage. Other factors such as hyperleukocytosis and DIC are the risk factors as well.^(4,5,11) In this study, four cases of hemorrhage had leukocyte counts over 100,000/mm³. Hemorrhage in these cases were from leukemic infiltration (Figure 4) in three and leukemic thrombi in one (Figure 5).

Features of leukemia involving various organs are described else-where.⁽¹⁾ Acute leukemia tends to infiltrate organs more frequently than chronic leukemia. Although the frequency of organ involvement is high, it seldom causes death itself. The most common organ failure as the cause of death is the heart in larger series.⁽⁵⁾ but not so in this study. Limited number of cases is the reason responsible. Excepting leukemia infiltration and previous illness such as coronary atherosclerosis, the other important cause of organ failure is chemotherapy which causes acute tumor lysis syndrome.⁽¹²⁾ The syndrome occurs when sensitive tumor cells such as leukemia and lymphoma undergo massive lysis after

receiving chemotherapy and results in multiple metabolic abnormalities together with renal failure. These features were noted in one of our cases.

In conclusion, causes of death in leukemia are still mainly infection and hemorrhage. The most important management of leukemia besides chemotherapy consists of supportive cares which include treatment of infection and prevention of fatal hemorrhage by transfusion therapy especially during the period of hypoplastic marrow. Chemotherapy, which is successful in treatment of the disease, is a double-edged sword for the patients since its complications are also fatal. Awareness of necrotizing enteritis and acute tumor lysis syndrome with early management of these complications is necessary to keep the patient alive.

Acknowledgement

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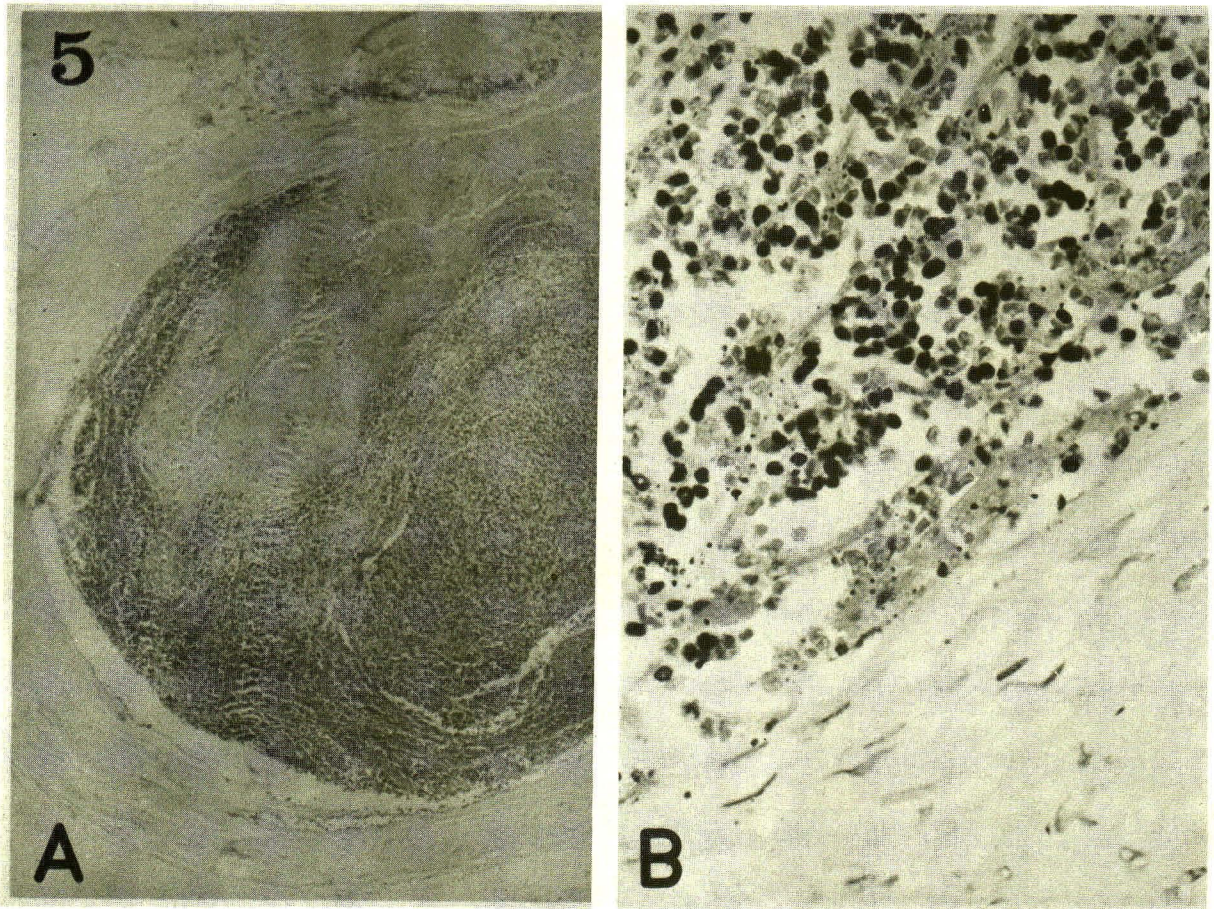


Figure 5. A. Left middle cerebral artery is occluded by leukemic cell-fibrin thrombus, H & E $\times 100$
 B. High Magnification of thrombus shows numerous leukemic cells and arterial wall, H & E $\times 400$

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