Original Articles

# Pathology diagnosis and discrepancy of marrow examination at Thammasat University Hospital

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## Abstract

**Introduction:** Pathology diagnosis based on histologic assessment of marrow is useful in establishing diagnosis, staging and monitoring treatment of various hematologic and non-hematologic diseases in clinical hematology practice. This study aimed to provide basic data for improvement of marrow diagnostic service.

**Method:** Pathology reports of 757 marrows were recruited from 1st August 2009 to 31st December 2011. The 262 cases were randomly chosen by systemic sampling for diagnosis review by another hematopathologist from different university hospital (third author). In case of discrepancy, the diagnosis was concluded by correlation with other laboratory tests, clinical information or additional ancillary tests.

**Result:** The indications for marrow biopsy were evaluation of malignancy 73.6%, abnormal CBC 20%, fever of unknown cause/infection 6% and rare congenital hematologic disease/metabolic disease 0.4%. Average turn around time was 2 days for initial diagnosis and 6 days for final diagnosis. Special stain and immunohistochemistry were done in 21.8% (average additional charge 43 Baht/case) and 29.8% of cases (average additional charge 564 Baht/case), respectively. Excluding the unsatisfactory specimen, the diagnoses reported were malignancy 23.3%, suspicious for malignancy 3.6%, infection 0.75%, non-neoplastic lesions 9.0%, reactive process 14% and no diagnostic abnormality 49.4%. Random review of the diagnosis detected kappa statistic of 89.6% with major discrepancy in 0.8% (2 cases). Both were false negative in detecting essential thrombocytosis and refractory anemia with excess blasts.

**Discussion and Conclusion:** Malignancy is prime concerned disease in pathology practice for being most common in indication, disease diagnosed and interpretation discrepancy. Marrow diagnostic service can be improved by clinical correlation, integrating multidisciplinary laboratory results, adequate specimen, good tissue preparation, morphologic diagnostic skill, special stains and immunohistochemical study.

**Key words:** Marrow, Pathology diagnosis, Discrepancy

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## Introduction

The histologic assessment in pathology diagnosis of marrow is useful in establishing diagnosis, staging, and monitoring treatment of various hematologic and non-hematologic diseases. The investigation is based on morphologic interpretation in correlation with indication and given clinical data. Special stains and immunohistochemistry are ancillary tests to identify chemical substance and specific antigen of certain diagnoses.

Pathology laboratory of Thammasat university hospital received more than 300 marrow specimens per year. The study collected informations from marrow pathology reports and randomly reviewed diagnoses for interpretative discrepancy.

The study aimed to provide basic data on indications, diagnoses, turn around time, special stains, immunohistochemistry and interpretative discrepancy for improvement of marrow histopathology diagnostic service.

## Method

This retrospective descriptive data collection recruited from pathology reports of all bone marrow core biopsy, marrow aspirate clot or marrow particle specimens at Pathology Laboratory of Thammasat university hospital examined between 1st August 2009 to 31st December 2011. These cases were interpreted by single hematopathologist in the early years of practice and laboratory expansion.

Indication was the reason or clinical impression for marrow evaluation, if given multiple the first in the list was collected. Diagnostic wording in pathology report ranged from specific disease entity such as plasma cell myeloma, lesion suspicious for neoplasm such as presence of dysplastic change suspicious for myelodysplastic syndrome, lesion supportive for diagnosis of non-neoplastic disorder such as marked hypocellularity in aplastic anemia, reactive change such as erythroid hyperplasia in response to peripheral destruction, and no diagnostic abnormality. The disease entity categories were malignancy, infection and non-neoplastic/non-infectious hematologic disorders.

Specimen was considered unsatisfactory for diagnosis when devoid of hematopoietic cell/marrow particle, marrow measuring less than 0.5 cm in length without lesion and presence of crush artifact/aspiration artifact/subcortical hypoplasia. These cases were excluded from random review.

Sample size (n) for random review of diagnoses was calculated according to Taro Yamane (Yamane, 1973) considering confidence interval of 95% and 5% sampling error by formula of n = N/(1 + Ne2). Where N (a population size) was 757, e (the level of precision at 95% confidence level) was 0.05, and n = 757/ [(1) + 757(0.05)2]. The sample size was no less than 262 cases.

The diagnoses were randomly reviewed by hematopathologist from another well established university hospital. These cases were randomly chosen by systemic sampling (random interval k = N/n; k = 757/262 = 3, thus case number 1st, 4th and so on). The cases with unsatisfactory specimen, no available slides and/or paraffin blocks were excluded for diagnosis reviewed. The reviewer evaluated H&E, PAS and ancillary stained slides with same provided clinical data. In case of interpretative disagreement, the diagnosis was concluded by correlation with available findings from marrow aspirate smear, flow cytometry, genetic tests, other laboratory tests, additional clinical data, follow up findings or further histologic ancillary tests.

Interpretive discrepancies were dividend in to 1) major when the change in diagnosis had clinical impact on treatment or prognosis eg. reversal of benign diagnosis to malignant, and 2) minor when minimal clinical relevance eg. no diagnostic abnormality reversal to presence of serous atrophy.

The study protocol was approved by human research ethics committee of Thammasat University.

## Result

Data collected from 757 specimens from 603 patients (320 females and 283 males, age range from 2 to 89 year-old, average age was 55 years and age below 16 years accounted for 6%). The purposes of marrow evaluation were for diagnosis 60%, staging of neoplasm 15% and monitor treatment 25%. The indications were evaluation of malignancy 73.6%, abnormal CBC 20%, fever of unknown

cause/infection 6% and rare congenital hematologic disease/ metabolic disease 0.4%.

Primary diagnostic evaluation of hematolymphoid neoplasm 33.5% comprised of myelodysplastic syndrome (MDS) 11.4%, plasma cell myeloma (PCM) 9.1%, myeloproliferative neoplasm (MPN) 5.8%, acute leukemia (AL) 5.4% and chronic lymphocytic leukemia (CLL) 0.8%.

Pathologic staging of neoplasms were for B-cell non-Hodgkin lymphoma (B-NHL) 7%, T-NHL 1.2% and HL 0.8%, lymphoma not specified type 5.2%, non-hematologic malignancy 0.8% and B-lymphoblastic lymphoma (B-LBL) 0.1%.

Assessments of disease status after therapy were done for acute myeloid leukemia (AML) 8.4%, MPN 4.5%, PCM 4%, acute lymphoblastic leukemia (ALL) 4%, B-NHL 1.4%, non-hematologic malignancy 1.4%, MDS 0.4%, HL 0.4%, T-NHL 0.4% and lymphoma and non-specified 1%.

Abnormal peripheral blood findings were pancytopenia/bicytopenia 9.7% (aplastic anemia AA 12 cases), anemia 5.5% (pure red cell aplasia PRCA 7 cases), thrombocytopenia 4% (immune thrombocytopenic purpura ITP 16 cases) and eosinophilia 0.5%.

Infectious disease assessment requested in 6.3% were fever of unknown origin 16, suspecting opportunistic infection in HIV infection 3.2%, systemic lupus erythematosus (SLE) 0.9%, febrile neutropenia 0.3%, chronic steroid usage 0.1 and congenital infection 0.1%.

Rare congenital hematologic diseases were Wiskott-Aldrich syndrome and Diamond Blackfan syndrome. The metabolic disease was amyloidosis.

Average turn around time, counting from date of receiving specimen, was 2 days for initial diagnosis and 6 days for final diagnosis.

Two hundred seventeen tests of special stains were done in 165 cases accounted for 21.8% of total cases. These stains were Perl Prussian blue 15%, AFB and GMS 5%, reticulin 0.8%, mucin 0.4% and Congo red 0.1%. Perl Prussian blue stain was done in cases of anemia, suspecting or known MDS to assess iron storage, distribution and ring sideroblast. Reticulin stain was done on myeloproliferative neoplasm cases to evaluate degree of fibrosis. Since the charge for special stain was 150 Baht per test, thus additional charge for special stains was 32,550 Baht for these 757 cases (average additional charge for staining 43 Baht/case).

Immunohistochemical staining added to 29.8% of the total cases composed of 787 tests and additional charge of 426,620 Baht (average additional charge for staining 564 Baht/case). The tests were CD34 32%, CD138/k/L 11.2%, CD3/CD20 10%, CD5/CD10/CD23/cyclin D1 2.9%, CD30 1.2%, AL lineage MPO/117/B/T 3.5%, T cell markers 0.8% and carcinoma markers 2.6%.

There were 410 cases (54%) that diagnoses were established based on morphology by H&E and PAS slides without special stain nor immunohistochemical study.

The unsatisfactory specimens for establishing diagnosis comprising 15.4% of total marrow were due to marrow size lesser than 0.5 cm 12.5%, absence of marrow 1.9%, aspiration artifact 0.5% and crushed artifact 0.5%.

Thirteen marrows measuring less than 0.5 cm in length were not excluded from the diagnosis data collection due to presence of AL 7 cases, PCM 2, abnormal megakaryocytes suspicious for MPN 1, abnormal megakaryocytes suspicious for MDS, fungus 1 and granuloma 1.

Based on 640 specimens, the reports were no diagnostic abnormality (NDA) 49.4%, reactive response 14%, lesion suggestive of non-neoplastic disorders of marrow 9% (iron deficiency 2.7%, ITP 2.5%, AA 2%, anemia of chronic disease 1.05%, PRCA 0.15% and granuloma 0.6%), infections 0.75% (tuberculosis 0.3%, atypical mycobacterium infection 0.15%, Cryptococcosis 0.15% and Histoplasmosis 0.15%) and suspicious for neoplasm 3.6% (MDS 1.9%, AL 0.8%, B-NHL 0.3%, T-NHL 0.3%, MPN 0.15%, and HL 0.15%).

Diagnosis of malignant neoplasms 23.3% were AL 9.2% (AML 1.25%, ALL 1.7%, AL no ancillary tests 6.25%), MPN 4.7% (CML 2.5%, ET 1.25%, PV 0.15%, MPN/MDS 0.3% and NOS 0.15%), MDS 1.05%, PCM 3.75%, B-NHL 3.3% (CLL 1.1%, DLBCL 1.1%, MZL 0.6%, MCL 0.3%, BL 0.15%), T-NHL 0.3%, CHL 0.15% and non-hematologic malignancy 0.8%.

The distributions of diagnoses from random 262 cases for review were similar to that of the 640 cases (Table 1).

**Table 1** Distribution of diagnoses from reviewed cases compared to satisfactory cases for diagnosis

| Diagnosis group | Satisfactory cases for diagnosis N = 640 (%) | Reviewed cases N = 262 (%) |
|---|---|---|
| Malignant neoplasm | 23.25 | 26.7 |
| Suspicious for malignancy | 3.6 | 5 |
| Non-neoplastic lesion and infection | 9 | 9.5 |
| Reactive response | 14 | 11.8 |
| No diagnostic abnormality | 49.4 | 46.9 |

The kappa statistic on inter-observer agreement in diagnosis in 262 cases was calculated (Table 2).

**Table 2** Pathology diagnosis agreement of marrow examination

| | Reviewer-Diagnosed | Reviewer-Not diagnosed | Total |
|---|---|---|---|
| Primary-Diagnosed | 98 (a) | 7 (b) | 105 (m1) |
| Primary-Not diagnosed | 9 (c) | 148 (d) | 157 (m0) |
| Total | 107 (n1) | 155 (n0) | 262 (n) |

Calculation

Expected agreement (Pe) = [(n1/n) x (m1/n)] + [(n0/n) x (m0/n)]
= [(107/262) x (105/262)] + [(155/262) x (157/262)]
= 0.403

Observed agreement (Po) = (a+d)/n
= (98+148)/262
= 0.938

Kappa (k) = (Po-Pe)/(1-Pe)
= (93.8-40.3)/(1-40.3)
= 0.89

Kappa statistic value 0.81-0.99 is considered almost perfect agreement. Random diagnosis review detected minor discrepancy 8 cases (3%) and major discrepancy 2 cases (0.8%).

The major discrepancy case 1 was a false negative in detecting ET. The original pathology report diagnosed as no diagnostic abnormality. ET was proven by correlation with clinical data, proliferation of abnormal megakaryocytes and presence of JAK-2 mutation. The discordance was due to under-recognition of morphology. Despite that, the patient received the treatment for ET in accordant with clinical data and genetic result. Comparison diagnosed cases and missed-diagnosed case, the later lacked clinical impression of ET and had focal morphology of ET (Table 3).

**Table 3** Comparison of data for bone marrow interpretation between diagnosed and missed diagnosed ET

| Data | Diagnosed ET N = 7 | Missed diagnosed ET N = 1 |
|---|---|---|
| Clinical suspision for ET | 7/7 | 0 (clinical PV with anemia vs. CML) |
| Platelet count ≥ 450,000 /uL | 7/7 | 1 (platelet count 700,000 /uL) |
| Satisfactory specimen | 6/7 (one case 0.4 cm in length) | 1 |
| Morphology-Proliferation of mature enlarged megakaryocytes | 7/7 | Presence in focal area |

The major discrepancy case 2 was false negative in detecting refractory anemia with excess blasts (RAEB). The original report was reported as hypercellular marrow due to trilineage hematopoiesis (reactive process). The reviewer detected dysplastic megakaryocytes in additional to original report. Additional CD34 marks scattered blasts representing 5-10%. Karyotype was not available. The patient lost to follow-up few months after marrow biopsy. This patient could had been closely followed up and received supportive treatment. Comparison of data for bone marrow interpretation between diagnosed and missed-diagnosed RAEB demonstrated that diagnostic skill and immunohistochemical study were required for establishment (Table 4).

**Table 4** Comparison of data for bone marrow interpretation between diagnosed and missed-diagnosed RAEB

| Data | Diagnosed RAEB N = 6 | Missed diagnosed RAEB N = 1 |
|---|---|---|
| Age > 50 YO | 4/6 (other two are 44 and 45 Yr) | 1 (61 Yr) |
| Cytopenia | 6/6 | 1 |
| Satisfactory specimen | 6/6 | 1 |
| Morphology-Dysplasia | 5/6 | Originally not recognized (reviewer detected dysplastic megakaryocytes) |
| BM blasts 5-19% | 6/6 | Originally not done (CD34 by IHC = 5-10% after review) |

The eight minor discordant cases were all false negative, from 4 NDA to presence of dysplastic megakaryocytes suspicious for MDS, 1 erythroid hyperplasia with comment of clinical and genetic correlation to supportive for PV, 1 myeloid hypoplasia to aplastic anemia, 1 NDA to serous atrophy of stromal fat and 1 NDA to reactive hypercellular marrow. The primary pathology diagnoses in these cases were descriptive and had to be correlated with other findings, thus did not effecting the treatment.

## Discussion and Conclusion

Detection of hematologic malignancy was the most common indication for marrow examination at Pathology lab of Thammasat University Hospital. And the most common disease group diagnosed in marrow tissue in this lab was also hematologic malignancy. In addition to that, the false negative interpretation leading to discrepancy was mainly malignancy (1 ET, 1 RAEB, 4 MDS and 1 PV).

WHO classification of tumors of hematopoietic and lymphoid tissues defined diseases by morphology, immunophenotype, genetic features and clinical information, and indicated "no one gold standard" by which one all disease are defined[1].

This study did not included additional expenses from recut H&E slide section. The cost for each special stains and immunohistochemical markers vary from lab to lab. Nevertheless, pathologist should have strong indication to order each ancillary tests.

Immunohistochemical staining added to 29.8% of the total cases composed of 787 tests and additional charge of 426,620 Baht (average additional charge for staining 564 Baht/case).

Under recognition of dysplastic megakaryocyte leaded to two major discordant cases (ET and RAEB) and five minor discordant cases (4 suspicious for MDS and 1 PV). Dysplastic megakaryocytes can be seen in myeloid malignancy such as MPN and MDS. Megakaryocyte cytomorphology is best assessed using both bone marrow aspirate smears and paraffin-embedded section in combination. Megakaryocyte in a healthy adult bone marrow is one to four per x40 magnification and remains individually dispersed at adjacent to bone marrow sinuses. The reactive megakaryocytes are evenly distributed throughout the marrow without cluster formation. Megakaryocyte dysplasia is characterized by micromegakaryocytes with hypolobated nuclei, nonlobated nuclei in megakaryocytes of all sizes, and multiple, widely separated nuclei. Significant megakaryocyte dysplasia is defined as $\geq$ 10% dysplastic megakaryocytes based on evaluation of at least 30 megakaryocytes in smears or sections. PAS and CD61 are helpful in detecting megakaryocytes, specially the small size with hypolobated nucleus.

ET is a chronic MPN involving primarily megakaryocytic lineage. It is characterized by sustained thrombocytosis $\geq$ 450x109/L in the peripheral blood (PB), increased numbers of large, mature megakaryocytes in the bone marrow and clinically by episodes of thrombosis and/or hemorrhage. The most striking abnormality in bone marrow is an increase in the number and the size of the megakaryocytes throughout the marrow, with giant megakaryocytes containing abundant mature cytoplasm and hyperlobated (stag-horn like) nuclei[2]. Although 50% of cases will have JAK2 V617F mutation[3], there is no genetic abnormality specific for ET[1]. All causes of thrombocytosis must be excluded before establishing diagnosis of ET.

PV is a chronic MPN characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis. Diagnosis of PV requires the presence of two major criteria and with two of minor criteria. The major criteria are 1) Hb > 18.5 g/dL in men, and 16.5 g/dL in women, or other evidence of increased red cell volume and 2) presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation. The minor criteria are 1) bone marrow showing trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation, 2) low serum EPO and 3) endogenous erythroid colony formation in vivo. In addition to morphologic criteria, the erythropoiesis occurs in expanded erythroid islands throughout marrow. Increased number of megakaryocytes is seen throughout marrow as clustering and usually lacking marked cytologic atypia. In addition to morphology, stainable iron is absent in more than 90% of cases[4].

MDS is a group of clonal hematopoietic stem cell disease characterized by cytopenia, dysplasia and ineffective hematopoiesis with increased risk of developing of AML. RAEB is a MDS with 5-19% myeloblasts in the bone marrow or 2-19% blasts in peripheral blood[1]. The diagnosis of MDS requires the integration of 1) clinical and hematologic data of unexplained and persistent cytopenia with exclusion of other causes, 2) morphologic findings of dysplasia ≥ 10% of cells in at least one hematopoietic lineage with blast enumeration and abnormal localization of immature precursors and 3) a clonal abnormal conventional karyotype[5]. About 50% of all MDS cases have an abnormal conventional karyotype[6]. Excellent marrow section, immunohistochemistry for CD34, myeloperoxidase and megakaryocyte markers are essential for assessment of dysplasia in myelodysplastic syndrome[7].

This study provided basic data for improvement of marrow histopathology diagnostic service. Interpreting marrow tissue based on given clinical data, morphology, special stain and immunophenotype resulted in discrepancy. Thus multidisciplinary approach with integration of clinical information, hematologic laboratory results, marrow aspirate smear findings, flow cytometry and genetic results would decrease error in establishing final diagnosis. Adequate marrow specimen by size and integrity is very important starting point of diagnosis. Laboratory techniques for good histologic section and development of further ancillary stainings are vital element for tissue diagnosis. Diagnostic skill enhancement could be gained through continuous education and practice, clinical hematopathology case conference and research on the routine practice.

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## บทคัดย่อ

**ผลการวินิจฉัยทางพยาธิวิทยาและความคลาดเคลื่อนของผลการวินิจฉัยชิ้นเนื้อไขกระดูกที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ**
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**บทนำ:** การตรวจวินิจฉัยชิ้นเนื้อไขกระดูกทางพยาธิวิทยาให้ข้อมูลที่สำคัญในการวินิจฉัย ประเมินระยะโรคและการรักษาโรคในเวชปฏิบัติทางโลหิตวิทยา การศึกษานี้รวบรวมข้อมูลพื้นฐานเพื่อนำไปพัฒนาบริการตรวจวินิจฉัยชิ้นเนื้อไขกระดูก

**วิธีการศึกษา:** ข้อมูลรวบรวมจากรายงานผลตรวจชิ้นเนื้อไขกระดูกทางพยาธิวิทยา ๗๕๗ ราย ตั้งแต่ ๑ สิงหาคม ๒๕๕๒ ถึง ๓๑ ธันวาคม ๒๕๕๔ และสุ่มทบทวนการวินิจฉัย ๒๖๒ ราย โดยพยาธิแพทย์จากโรงพยาบาลอื่น เพื่อศึกษาความคลาดเคลื่อน กรณีพบความคลาดเคลื่อนจึงทำการสรุปผลการวินิจฉัย โดยพิจารณาผลตรวจจากห้องปฏิบัติการอื่นร่วมกับข้อมูลคลินิกหรือการติดตามโรคและการย้อมเพิ่มเติม

**ผลการศึกษา:** ข้อบ่งชี้ในการตรวจชิ้นเนื้อไขกระดูกประกอบด้วย สงสัยมะเร็ง ร้อยละ ๗๓.๖ ความสมบูรณ์ของเม็ดเลือด (CBC) ผิดปรกติ ร้อยละ ๒๐ ไข้ไม่ทราบเหตุหรือสงสัยโรคติดเชื้อ ร้อยละ ๖ และโรคโลหิตวิทยาแต่กำเนิดที่พบไม่บ่อย ร้อยละ ๐.๔ ระยะเวลาในการรายงานผลเบื้องต้นเฉลี่ย ๒ วันและผลสมบูรณ์เฉลี่ย ๖ วัน มีการย้อมพิเศษ ร้อยละ ๒๑.๘ (ถัวเฉลี่ยค่าย้อมเพิ่ม ๔๓ บาทต่อราย) และย้อมอิมมูโนฮีสโตเคมี ร้อยละ ๒๙.๘ (ถัวเฉลี่ยค่าย้อมเพิ่ม ๕๖๔ บาทต่อราย) ชิ้นเนื้อที่ส่งตรวจและมีคุณภาพเพียงพอต่อการวินิจฉัยพบเป็นมะเร็ง ร้อยละ ๒๓.๓ สงสัยมะเร็ง ร้อยละ ๓.๖ โรคติดเชื้อ ร้อยละ ๐.๗๕ รอยโรคที่ไม่ใช่มะเร็ง ร้อยละ ๙ ปฏิกิริยาตอบสนอง ร้อยละ ๑๔ และไม่พบความผิดปรกติ ร้อยละ ๔๙.๔ การสุ่มทบทวนผลการวินิจฉัยพบสถิติ kappa ร้อยละ ๘๙.๖ และพบความคลาดเคลื่อนอย่างมีนัยสำคัญทางคลินิก ร้อยละ ๐.๘ (๒ ราย) ซึ่งเป็นรายที่ควรได้รับการวินิจฉัยว่าเป็น essential thrombocytosis และ refractory anemia with excess blasts

**วิจารณ์ และสรุปผลการศึกษา:** มะเร็งเป็นกลุ่มโรคที่สำคัญที่สุดในการตรวจวินิจฉัยทางพยาธิวิทยาชิ้นเนื้อไขกระดูก เพราะเป็นข้อบ่งชี้และเป็นโรคที่ได้รับการวินิจฉัยบ่อยที่สุด ประกอบกับพบความคลาดเคลื่อนอย่างมีนัยสำคัญ การวินิจฉัยไขกระดูกทางพยาธิวิทยาต้องอาศัยข้อมูลทางคลินิก สิ่งส่งตรวจและสไลด์ชิ้นเนื้อที่มีคุณภาพ ทักษะในการวินิจฉัยของพยาธิแพทย์ การย้อมพิเศษและการย้อมอิมมูโนฮีสโตเคมี

**คำสำคัญ:** ไขกระดูก, การวินิจฉัยทางพยาธิวิทยา, ความคลาดเคลื่อน