

Hematopoietic cells: Clues to diagnosis in surgical neuropathology

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Neuropathology is often viewed by many general pathologists as formidable area in pathology. Therefore, there is a need to identify simple histological clues, which every pathologist can recognize. Interestingly, many lesions of the nervous system contain a significant proportion of normal hematopoietic cells, such as neutrophils, lymphocytes, eosinophils, plasma cells, histiocytes, and mast cells. In this special article, the author summarizes conditions of the nervous system that are associated with proliferations of these cells. Identification of hematopoietic cells in the lesions of the nervous system should guide pathologists to the correct diagnosis.

Keywords: Hematopoietic cells, Nervous system, Surgical neuropathology.

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Objective :

For enabling general pathologists to identify simple diagnostic clues for the diagnosis of surgical neuropathology.

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จุฬาลงกรณ์เวชสาร 2546 ต.ค; 47(10): 619 - 28

ประสาทพยาธิวิทยาเป็นสาขาทางพยาธิวิทยาที่พยาธิแพทย์ทั่วไปส่วนใหญ่ไม่คุ้นเคย จึงมีความจำเป็นที่จะต้องหาการเปลี่ยนแปลงทางพยาธิสภาพที่สามารถตรวจพบได้ง่าย และพยาธิแพทย์ทุกคนรู้จัก เป็นที่น่าสนใจว่ารอยโรคทางระบบประสาทไม่น้อย พบมีการเพิ่มจำนวนของเซลล์เม็ดเลือดชนิดต่าง ๆ อาทิเช่น นิวโทรฟิล ลิมโฟไซต์ ฮีโมสโตไนท์ พลาสมาเซลล์ ฮีสติโอไซต์ และมาสเซลล์ ในบทความพิเศษนี้ผู้เขียนได้รวบรวมรอยโรคต่าง ๆ ของระบบประสาท ที่พบมีการเพิ่มจำนวนของเซลล์เม็ดเลือดเหล่านี้ การตรวจพบเซลล์เม็ดเลือดในรอยโรคของระบบประสาท น่าจะมีส่วนช่วยชี้นำพยาธิแพทย์ให้ไปสู่การวินิจฉัยที่ถูกต้อง

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย



To arrive at the correct pathological diagnosis, it is not always a straightforward matter. The prerequisite for this is that the pathologists need to know or have heard about the disease that he or she is facing. However, because of a wide range of diseases and morphological overlaps, it is not an easy task to be up-to-date in all fields of pathology. In particular, neuropathology is one of the subjects in pathology that most of the general pathologists are unfamiliar with. Therefore, there is a need to identify simple histological clues, every pathologist can recognize that lead to the correct answer.

Interestingly, many lesions of the nervous system contain a significant proportion of hematopoietic cells, well-known to all pathologists. In many circumstances, there are no clues that explain why those cells appear or what the function of the cells is in the neural lesions. Nevertheless, they are important histological hints, which should help pathologists formulate the differential diagnosis and, in many cases, arrive at the final diagnosis. Herein, conditions of the nervous system that are associated with proliferations of hematopoietic cells are summarized. (Table 1.)

Table 1. Summary of neural diseases associated with proliferation of hematopoietic cells.

Hematopoietic Cells	Diseases	Frequency
Neutrophils	Tumors	- / +
	Any tumors with necrosis	
	Non-tumors	
	Bacterial infection e.g. meningitis, abscess	++
	Fungal infection	- / +
	Tuberculous infection	- / +
Lymphocytes	Ischemic/hypoxic	- / +
	Tumors	
	Glioma	- / +
	Ganglioglioma	+ / -
	Germinoma	++
	Non-tumors	
	Viral infection	+
	Tuberculous infection	+
	Demyelinating disease	+
	Vasculitis	+
Chronic and subacute inflammation	+	
Eosinophils	Tumors	
	Langerhans cell histiocytosis	+ / -
	Hodgkin disease	+ / -
	T-cell lymphoma	+ / -
	Non-tumors	
	Parasitic infection	++
	Chronic subdural hematoma membrane	- / +

Table 1. Continuous.

Hematopoietic Cells	Diseases	Frequency
Plasma cells	Tumors	
	Lymphoplasmacyte-rich meningioma	++
	Rosai-Dorfman disease	+
	Plasma cell tumor	++
	Chordoid glioma of the 3 rd ventricle	+/-
	Non-tumors	
	Chronic and subacute inflammation	+
Plasma cell granuloma	++	
Foamy histiocytes	Tumors	
	High-grade glioma with necrosis	-/+
	Schwannoma	-/+
	Non-tumors	
	Reactive gliosis	+/-
	Demyelinating disease	+/-
	Xanthogranuloma	++
Epithelioid histiocytes	Tumors	
	Germinoma	-/+
	Hodgkin lymphoma	-/+
	T-cell lymphoma	-/+
	Non-tumors	
	Infection e.g. tuberculosis, fungus, amebic.	+
	Granulomatous vasculitis	+
	Giant cell granulomatous hypophysitis	++
Sarcoidosis	++	
Mast cells	Tumors	
	Meningioma	+
	Hemangioblastoma	+
	Subependymal giant cell astrocytoma	+
	Neurofibroma	+

Neutrophils (Polymorphs)

Neutrophils are leukocytes with multi-lobed shape of their nucleus. Two types of granules are present in the cytoplasm of neutrophils including specific and azurophilic granules, but they are invisible on routine hematoxylin and eosin (H&E) stain. Marked proliferation of neutrophils is the atypical feature of acute suppurative (purulent) inflammation, as seen in bacterial infection, either in the form of meningitis, subdural empyema or abscess (Fig. 1).

Fungal infection is sometimes associated with neutrophilic proliferation. Rarely, tuberculous infection presents with abscess, morphologically similar to that of the bacterial.⁽¹⁾ Apart from the purulent inflammation, it should be noted that neutrophils also migrate, to lesser extent, into the areas where necrotic tissue is. Therefore, it is not surprising that neutrophils could be found in ischemic/hypoxic lesions such as infarct, and other types of necrosis, including necrosis in tumors.

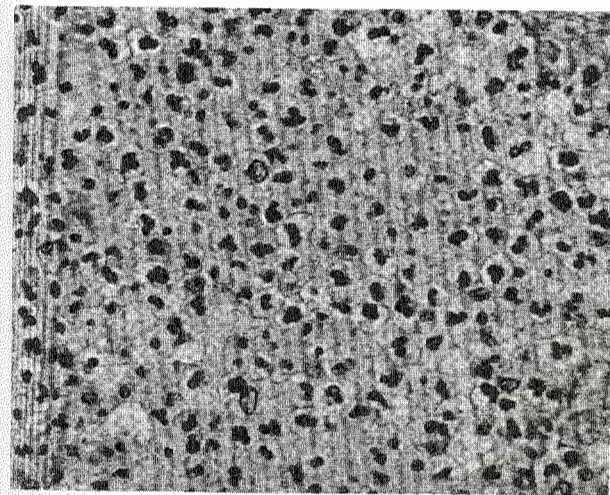


Figure 1. Aggregate of neutrophils in nocardial brain abscess is depicted (H&E).

Lymphocytes

Lymphocytes are small round lymphoid cells, with mildly indented nuclei and scant cytoplasm. Increased number of lymphocytes in the subarachnoid space suggests viral and tuberculous meningitis. Although the presence of lymphocytes in the neural tissue, particularly in a form of perivascular cuffing,

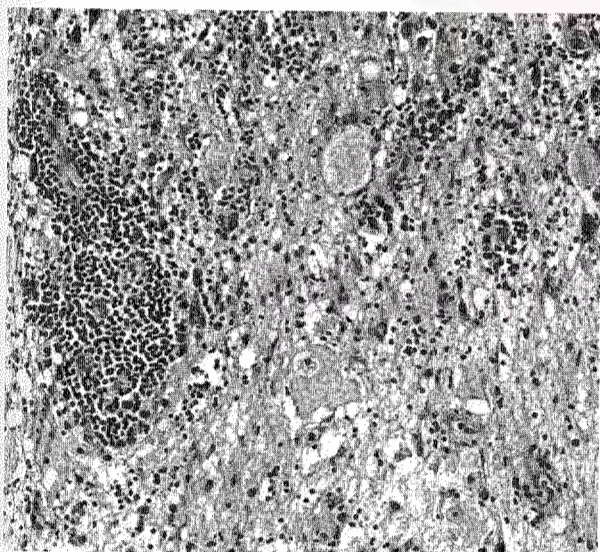


Figure 2. Though typically present in inflammatory process, perivascular infiltrates of lymphocytes can be observed in neoplastic lesions as in this example of ganglioglioma (H&E stain).

features inflammatory lesions namely viral encephalitis or demyelinating lesions, this perivascular arrangement is rather nonspecific as it could also be observed in several neoplastic entities, including diffuse astrocytoma, pleomorphic xanthoastrocytoma and ganglioglioma (Fig. 2).⁽²⁾ Infiltrates of lymphocytes into the vascular wall with damage to the vessel should prompt a consideration of vasculitis, either the primary or the secondary form. In germinoma, lymphocytes constitute the second cellular population, creating the characteristic of bimodal population of the lesion.

Eosinophils

Eosinophils have a bi-lobed nucleus and contain brightly eosinophilic cytoplasmic granules. They are readily appreciated on routine H&E stain. In the nervous system, increased number of eosinophils is well-known to be associated with parasitic infection. Nevertheless, it should be kept in mind that they could also be encountered in other conditions.

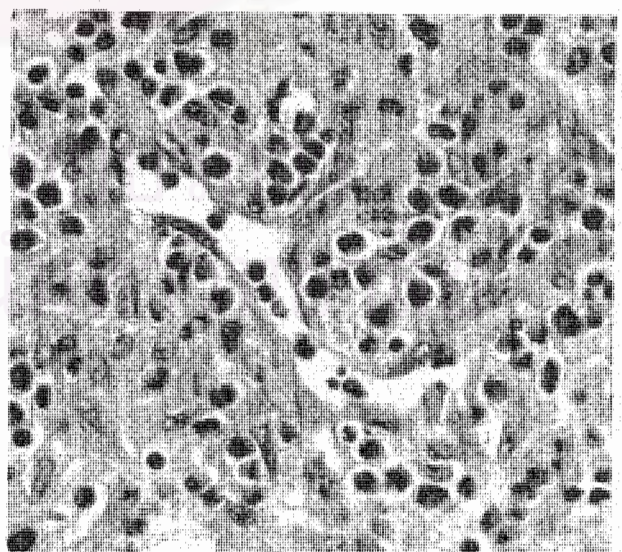


Figure 3. Proliferation of eosinophils are occasionally seen in the granulation tissue of chronic subdural hematoma membrane (H&E stain).

Notably, reactive eosinophils are typically present in Langerhans cell histiocytosis.⁽³⁾ Therefore, the diagnostic Langerhans histiocyte should be looked for, especially when the clinical features are suggestive of the diagnosis. Enigmatically, eosinophils have also been found in the membrane of chronic subdural hematoma (Fig 3).⁽⁴⁾ Hodgkin disease and T-cell lymphoma frequently contains eosinophils,⁽³⁾ but they rarely affect the nervous system.^(5,6) The presence of immature eosinophilic metamyelocytes, with banded nuclei, should raise the possibility of granulocytic sarcoma.^(3,7)

Plasma Cells

Plasma cells possess round to ovoid, eccentrically-placed nucleus, with typical clock-faced chromatic pattern. The cytoplasm is amphophilic and shows perinuclear cytoplasmic pale zone, known as perinuclear hoff. Plasma cells are frequently seen in chronic or subacute inflammation. Nonetheless, proliferation of plasma cells is also observed in many tumors and tumor-like conditions. Dural-based lesions with prominent plasma cells include lymphoplasmacyte-rich meningioma,⁽⁸⁾ Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy),^(9,10) and plasma cell granuloma.⁽¹¹⁾ Lymphoplasmacyte-rich meningioma is a variant of meningioma, which contains numerous lymphoplasmacytic cells. Inflammatory cells may predominate and obscure tumor cells. Hence, care is needed to search for the diagnosis of menigothelial components. Rosai-Dorfman disease (Fig. 4) sometimes affects the nervous system. The lesions typically contain numerous lymphocytes and plasma cells. Large histiocytes with acquired

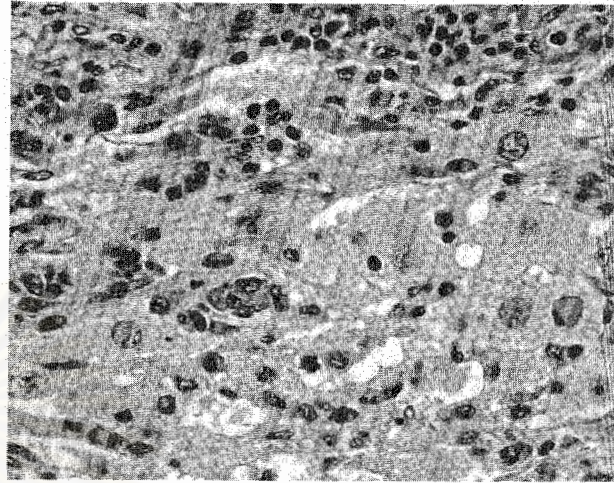


Figure 4. Plasma cells and lymphocytes in meningioma Rosai-Dorfman disease is illustrated. Note a few large histiocytes with emperipolesis (H&E stain).

lymphoplasmacytic cells in the cytoplasm (referred to as “emperipolesis”) is the diagnostic hallmark of this idiopathic histiocytic proliferation. Rarely, accumulation of reactive plasma cells forms a tumor-like lesion, plasma cell granuloma. A recently-described chordoid glioma of the third ventricle often contains plasmacytic infiltration.⁽¹²⁾ Plasma cell tumors, both plasmacytoma/multiple myeloma, should be considered for a lesion with numerous plasma cells. Monotonous infiltrates of plasma cells, with a light chain restriction on immunohistochemical study, support the neoplastic nature.^(9,10)

Foamy Histiocytes

Foamy histiocytes are characterized by lentiform vesicular nuclei, with abundant foamy pale eosinophilic cytoplasm. Unlike epithelioid histiocytes (see below), they have distinct cell boarder. Foamy histiocytes are scavenger cells, which remove all kinds of debris. One of the top differential diagnoses in neuropathology is to distinguish between glioma,

particularly the low-grade lesion, and reactive gliosis from various etiologies. The presence of foamy histiocytes is one of the important features that favor the reactive condition.⁽²⁾ Nonetheless, it should also be emphasized that foamy histiocytes could be found in high-grade gliomas, presumably due to the presence of necrosis. Demyelinating disease may mimic tumor, clinically and radiologically. Again, a demyelinating lesion generally contains a large number of foamy histiocytes. Lastly, foamy macrophages are commonly found in tumors and tumor-like conditions, particularly schwannoma (Fig. 5),⁽¹³⁾ and xanthogranuloma.⁽¹⁴⁾

Epithelioid Histiocytes

Epithelioid histiocytes are transformed histiocytes, which appear epithelial-appearing. They have oval-shaped vesicular nuclei, and abundant pale eosinophilic cytoplasm with indistinct cytoplasmic membrane. Sometimes, several epithelioid histiocytes

assembly to form multinucleated giant cells. The aggregate of epithelioid histiocytes is known as granuloma. Even though the prototype of granulomatous is tuberculous infection, other inflammatory processes characterized by granulomatous inflammation include fungal (Fig. 6), amebic and parasitic infections, and granulomatous angiitis. Non-caseating granuloma is found in sarcoidosis, which sometimes involves the nervous system as isolate disease.⁽¹⁵⁾ The idiopathic granulomatous inflammation of pituitary region is referred to as giant cell granulomatous hypophysitis.⁽¹⁶⁾ It has been recommended that care should be taken to search for the diagnostic germinoma cells if granuloma is present in the pineal or the suprasellar regions, where the germ cell tumor frequently arises.⁽¹⁷⁾ Particular types of malignant lymphoma including Hodgkin disease and T-cell lymphoma may also create granulomatous response.⁽³⁾

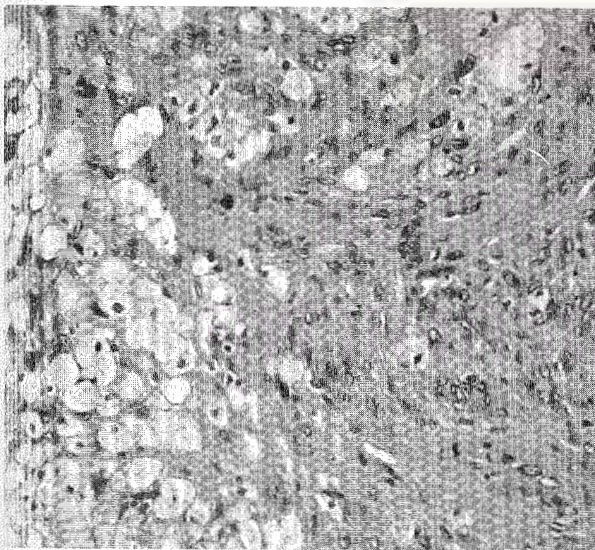


Figure 5. Aggregates of foamy histiocytes in a vestibular schwannoma is shown (H&E stain).

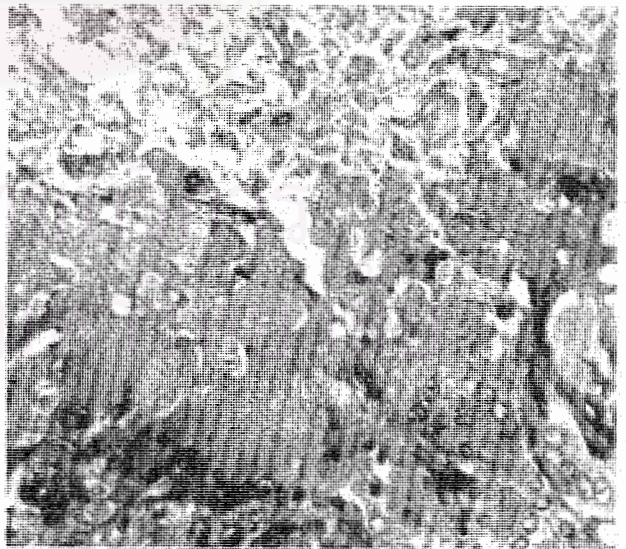


Figure 6. Granuloma of the sellar region with necrosis is demonstrated (H&E stain). Note multinucleated giant cells. This granulomatous inflammation is due to fungal infection; the organisms are morphologically consistent with aspergillosis.

Mast Cells (Tissue Basophils)

Mast cells have leniform vesicular nuclei, with pale homogenously eosinophilic cytoplasm. They are, thus, difficult to discern in routine stain. Toluidine blue or Giemsa stain is necessary to demonstrate mast cell granules. Meningioma is known to contain mast cells,⁽¹⁸⁾ but in practice the diagnosis of meningiothelial neoplasms can be made without identification of the cell. For unknown reason, mast cells are also present in hemangioblastoma.⁽¹⁹⁾ Detection of mast cells is, indeed, an important diagnostic clue for intra-operative diagnosis by squash technique.⁽²⁰⁾ Mast cells have also been demonstrated in subependymal giant cell astrocytoma (SEGA),⁽¹⁸⁾ the finding that may differentiate SEGA from other astrocytic tumors, especially the high-grade lesions. The presence of mast cells in neurofibroma (Fig. 7) is also a helpful feature to discriminate the nerve sheath tumor from dermatofibroma.⁽²¹⁾

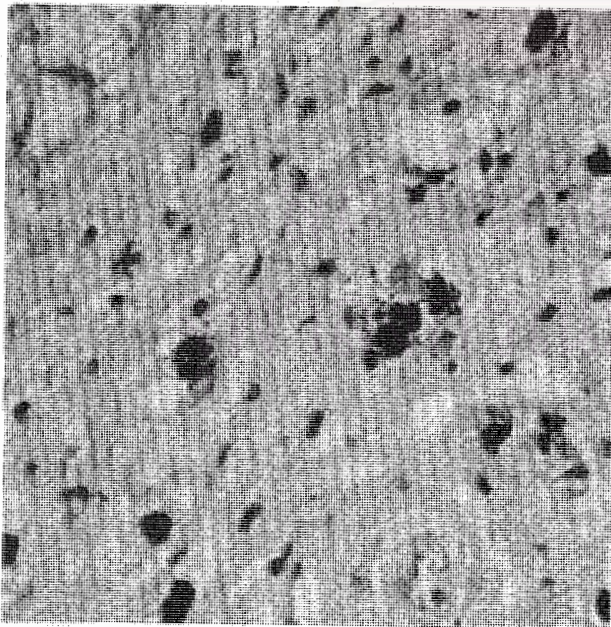


Figure 7. Mast cells are scattered in plexiform neurofibroma (Toluidine blue stain).

Conclusion

Neural diseases associated with proliferation of hematopoietic cells have been summarized. Recognition of these cells should provide clues to diagnosis in surgical neuropathology. Nevertheless, it should be emphasized that "clues to diagnosis are just clues". Identification of these clues should hint to the correct answer, but they are not entirely pathognomonic. Most of the time, the final diagnosis is not based on a single finding, but rather on all of the pathological changes. Clinical correlation is always important, but it is often neglected by both the pathologists and the clinicians, unfortunately.

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สถาบันวิทยบริการ จุฬาลงกรณ์มหาวิทยาลัย

กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง "เซลล์เม็ดเลือด : สิ่งชี้้นำในการวินิจฉัยทางพยาธิวิทยาของโรกระบบประสาท" โดยตอบคำถาม ข้างล่างนี้ ที่ท่านคิดว่าถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจจำนวนเครดิตได้จาก <http://www.ccme.or.th>

คำถาม - คำตอบ

- The following lesions typically contain mast cells except
 - Hemangioblastoma
 - Neurofibroma
 - Neurilemmoma
 - Subependymal giant cell astrocytoma
 - Meningioma
- Eosinophils are frequently encountered in the following lesions except
 - Cysticercosis
 - Langerhans cell histiocytosis
 - Chronic subdural hematoma
 - Rosai-Dorfman disease
 - Hodgkin disease
- Epithelioid granuloma can be observed in the following lesions except
 - Germinoma
 - B-cell lymphoma
 - T-cell lymphoma
 - Hodgkin disease
 - Sarcoidosis

คำตอบ สำหรับบทความเรื่อง "เซลล์เม็ดเลือด : สิ่งชี้้นำในการวินิจฉัยทางพยาธิวิทยาของโรกระบบประสาท"

จุฬาลงกรณ์เวชสาร ปีที่ 47 ฉบับที่ 10 เดือนตุลาคม พ.ศ. 2546

รหัสสื่อการศึกษาต่อเนื่อง 3-15-201-9010/0310-(1042)

ชื่อ - นามสกุลผู้ขอ CME credit เลขที่ใบประกอบวิชาชีพเวชกรรม.....

ที่อยู่.....

1. (a) (b) (c) (d) (e)

4. (a) (b) (c) (d) (e)

2. (a) (b) (c) (d) (e)

5. (a) (b) (c) (d) (e)

3. (a) (b) (c) (d) (e)

4. The presence of foamy histiocytes argues against which of the following diagnoses?
- Low-grade diffuse astrocytoma
 - Multiple sclerosis
 - Cerebral infarct
 - Reactive gliosis
 - Schwannoma
5. Which of the following lesions contains plasma cells with light chain restriction?
- Rosai-Dorfman disease
 - Chordoid glioma of the third ventricle
 - Plasmacytoma
 - Plasma cell granuloma
 - Lymphoplasmacyte-rich meningioma

เฉลย สำหรับบทความ รหัสสื่อการศึกษาต่อเนื่อง 3-15-201-2003/0309-(1040)

1. ค 2. ข 3. ง 4. จ 5. ก

เฉลย สำหรับบทความ รหัสสื่อการศึกษาต่อเนื่อง 3-15-201-2003/0309-(1041)

1. c 2. b 3. c 4. d 5. e

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จุฬาลงกรณ์มหาวิทยาลัย

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit)
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