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Unveiling Cancer

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إزاحة الستار عن السرطان

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ABSTRACT: This article narrates a multifaceted educational journey undertaken by a medical student through a weekly SCRAPS (surgery, clinical disciplines, radiology, anatomy, psychiatry and laboratory sciences) clinico-pathological meeting held in the College of Medicine & Health Sciences at Sultan Qaboos University in Muscat, Oman. Through a presentation titled 'Unveiling Cancer', the multidisciplinary and interprofessional audience witnessed a simulated interaction between a medical student, a technologist peer and tutors in medicine, pathology and radiology. The presentation was based on the complexities of presentation, diagnosis and management of a patient with anaplastic large cell lymphoma, a rare type of non-Hodgkin lymphoma, in the aftermath of a bone marrow transplantation. After describing the case, the student shared with the audience a spectrum of learning objectives, which included integration in the complex world of contemporary medicine, insight into the triumphs and travails of technology (immunohistochemistry) and peer collaboration, communication and mentorship.

Keywords: Clinico-Pathological Conference; Anaplastic Large-Cell Lymphoma; Immunohistochemistry; Medical Education; Oman.

الملخص: يصف هذا المقال رحلة علمية متعددة الجوانب قام بها طالب طب في ملتقى عيادي–باثولوجي يعقد أسبوعيا في كلية الطب والعلوم الصحية في جامعة السلطان قابوس في مسقط بعمان لتقديم محاضرات وحالات مرضية في علوم الجراحة والمواد العيادية والأشعة والتشريح والأمراض العصبية والنفسية وعلوم المختبرات (يعرف اختصارا بـ SCRAPS). وفي ذلك الملتقى قدم الطالب للحضور (وهم من تخصصات علمية ومهنية مختلفة) محاضرة بعنوان "إزاحة الستار عن السرطان" أتاحت فرصة طيبة لإثارة تفاعل بين طالب طب وأحد الأقران من الفنيين وأساتذة في الطب والأشعة وعلم الأمراض. وكان أساس المحاضرة المقدمة يعتمد على التعقيدات في عرض الحالة وتشخيصها وأسلوب معالجتها في مريض كان مصابا بسرطان الغدد اللمفاوية الكشمي اللاهودجكيني كبيرة الخلية (وهي نوع نادر الحدوث من اللمفوما اللاهودجكينة) حدثت نتيجة لنقل نقي العظام. وبعد أن قدم الطالب الحالة أشرك الطالب الحاضرين في طيف من أهداف التعلم والتي شملت التكامل في عالم معقد من الطب العصري، وتبصر نافذ في انتصارات وإخفاقات التقنية (الكيمياء الهيستولوجية المناعية)، والتعاون بين الزملاء والأقران والتواصل والإرشاد.

مفتاح الكلمات: ملتقى عيادي–باثولوجي؛ لمفومة كشمية لاهودجكينة كبيرة الخلية؛ الكيمياء الهيستولوجية المناعية؛ التعليم الطبي؛ عمان.

The acronym 'SCRAPS' stands for surgery, clinical disciplines, radiology, anatomy, psychiatry and laboratory sciences and it is the name of a weekly clinico-pathological forum held at the College of Medicine & Health Sciences (COMHS) at Sultan Qaboos University (SQU) in Muscat, Oman. The forum is a one-hour interdisciplinary presentation of clinical cases with educational value for faculty and clerkship students, usually steered by divisions of medicine and surgery with diagnostic input. In a significant diversion from this practice, a pathology-led SCRAPS session was used to focus on a triumvirate that is the foundation of 21st century academic clinical practice, in a presentation called 'Unveiling Cancer'. Firstly, its educational objective aimed at unifying and dissecting the complexities and challenges of disease arising from advances in therapy and technology.[1] Secondly, it offered an insightful analysis of the triumphs and travails of technology, using immunohistochemistry (IHC) as an example. Thirdly, it highlighted the interdependency and need for dialogue among interdisciplinary and interprofessional health providers. The whole exercise was designed to simulate the learning journey undertaken by a medical graduate in a clinical scenario, mentored by a team of educators, which unfolded in a staged format to engage the audience.[2]

At the Bedside

A junior clerkship student presented a patient's clinical profile to his physician-educator.

A 24-year-old male patient presented with a two-week history of shortness of breath on mild exertion. There was no history of cough, chest pain or palpitations, nor was there any recent history of fever or weight loss. However, he had noticed a mass in

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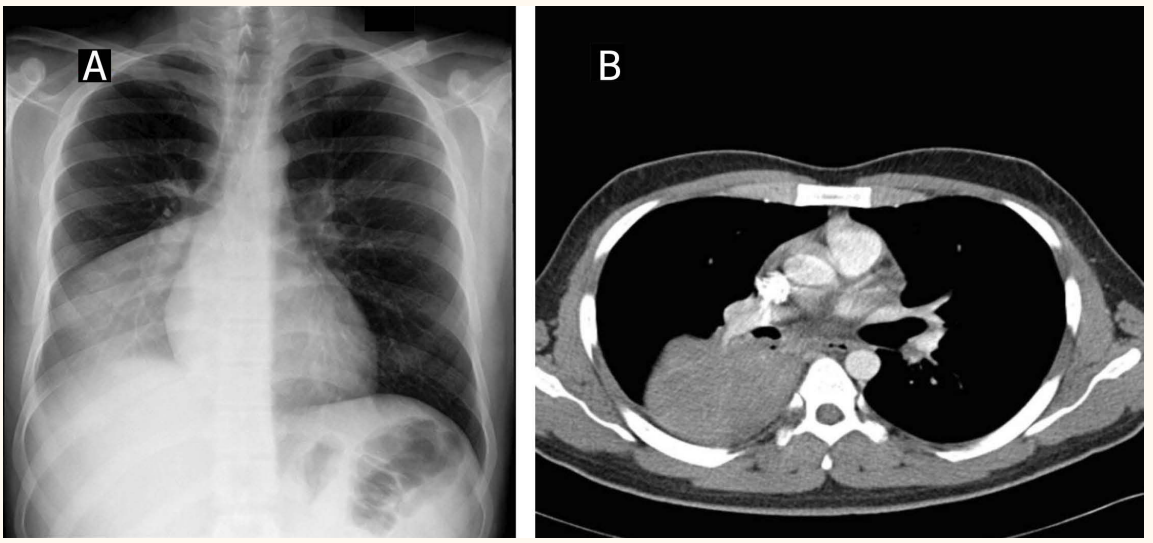

Figure 1A & B: Chest imaging (**A**) X-ray and (**B**) computed tomography scan showing a right lower lobe collapse and endobronchial mass.

the left thigh over the past one month. The patient had undergone an allogeneic bone marrow transplant (BMT) for thalassaemia major 12 years previously, using high doses of alkylating agents as conditioning chemotherapy. On examination, he was a fit young man, not pale or icteric and with no peripheral lymphadenopathy. A respiratory system examination revealed he had reduced chest movement, a dull percussion note, reduced breath sounds and an increased vocal *fremitus* on the right side in the lower third of the chest. He was not anaemic but had polymorphonuclear leucocytosis and thrombocytosis. The prothrombin time showed a mild increase in the international normalised ratio.

Shadows of Disease

The radiologist recounted the salient imaging findings for the audience.

An X-ray of the chest revealed a right lower lobe collapse, confirmed via computerised tomography of the chest, abdomen and pelvis [Figure 1]. A small soft tissue mass was seen projecting within the lumen of the right bronchus *intermedius* with no significant focal enhancement. There was no significant thoracic or abdominal lymphadenopathy. The right adrenal gland showed an irregular 2 x 3.4 cm well-defined internally degenerated mass with mural enhancement. A bronschoscopy revealed an endobronchial mass.

Magnetic resonance imaging of the left thigh revealed an oval solid mass (15.7 x 6.3 cm) in the medial aspect of the lower half of the thigh, engulfing the belly of the *gracilis* muscle, extending and splaying the adductor *magnus* and sartorius muscles; it showed heterogenous enhancement. The neuro-vascular bundle and bones were free. Overlying skin and subcutaneous tissue were thickened. A diagnosis of sarcoma was suggested, requiring confirmation by biopsy [Figure 2].

The student analysed the case and suggested to the tutor that the two masses probably had the same aetiology. The physician and student debated the biopsy diagnosis of the endobronchial mass and the thigh mass, which had been categorised as small round blue cell tumours (SRCT). Following immunophenotyping, the former was diagnosed as a primitive neuroectodermal tumour (PNET) and the latter as an anaplastic large cell lymphoma (ALCL). The student expressed uncertainty in comprehending the application of IHC that led to these divergent diagnoses. The physician suggested that the student solve this dilemma by going to the laboratory to acquire clarity on the concepts of usage and interpretation of IHC.

A Quest for Knowledge

The student approached his former pathology teachers to fill the gaps in his knowledge.

The pathologist-educator was surprised and delighted with the young student's sense of purpose in resolving clinical applications of laboratory techniques. She recommended a short 'back to basics' tutorial on the principles of IHC to the medical clerk, provided by the student's biomedical sciences peer, in order to initiate his understanding of IHC. The technologist-student succinctly explained it as an application of the immunologic principle of antigen-antibody reaction on tumour tissues. In tumours which are poorly differentiated on morphology, the antigenic

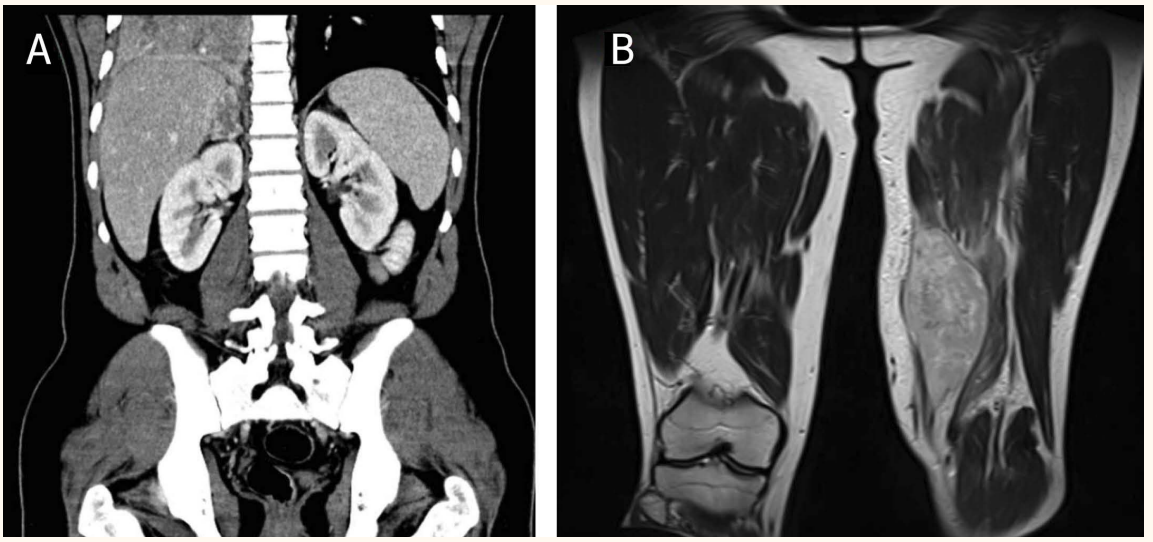

Figure 2A & B: A: Computed tomography scan of the abdomen, showing an irregular mass in the right adrenal gland. **B:** Magnetic resonance imaging of the thigh, showing a large oval solid soft tissue mass in the medial aspect of the lower thigh.

fidelity in specific tumours could be identified *in vitro* by the application of the corresponding antibody on sections of the tumour tissue, thus 'unveiling' its histogenetic differentiation. This, in turn, would direct the choice of therapy or provide an insight into the tumour's biological behaviour.

Armed with this knowledge the medical student proceeded to meet the reporting pathologist to demystify the two divergent diagnoses rendered in the patient.

The 'Final' Diagnosis

The reporting pathologist listed a short differential diagnosis for SRCT in this young adult including rhabdomyosarcoma, non-Hodgkin lymphoma (NHL), Ewing's sarcoma/PNET and small cell (neuroendocrine) carcinoma. He illustrated a 'shopping cart' of antibodies, from which a panel was selected to 'unveil' the poorly differentiated tumour in the patient [Figure 3]. The first biopsy, in a small and crushed sample (bronchial mass), showed immunoreactivity to cluster of differentiation (CD) 99 and CD30 and was negative for leukocyte common antigen (LCA; a commonly employed lymphoma marker); hence the PNET interpretation. The second larger and better preserved biopsy (the thigh mass) showed positivity for the previous two antigens as well as additional markers: anaplastic lymphoma kinase (ALK)-1 and CD43 [Figure 4]. This led to a final diagnosis of ALCL. Both masses represented ALCL on final review.

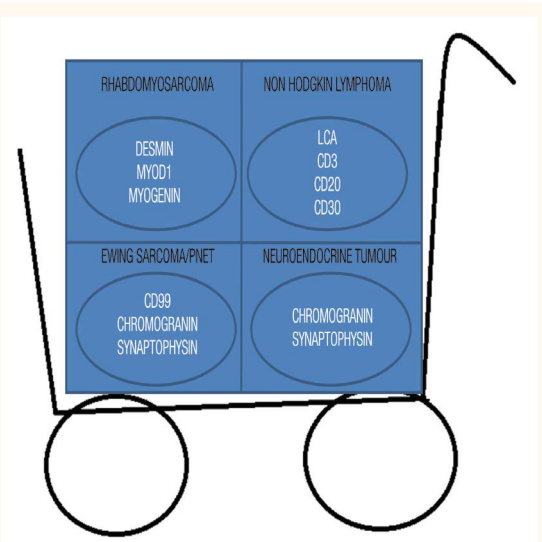

Figure 3: Shopping cart illustrating the panel of antibodies used for immunophenotypic characterisation of the biopsies from the bronchial and thigh masses.

LCA = leukocyte common antigen; MYOD1 = myoblast determination protein 1; CD = cluster of differentiation.

With this patient as an example, the pathologist listed several pitfalls in the contextual interpretation of IHC: small and poorly preserved tissue resulted in a challenge for interpretation; the primary site would have been the better and more reliable biopsy source for antigenic expression; antibodies like CD99 are cross-reactive with other tumours; and LCA, which is usually expressed in lymphoid cells, is negative in ALCL (a rare type of lymphoma).[3–5] He also explained that ALK immunohistochemical positivity in ALCL was due to the abnormal accumulation of a chimeric protein due to a *nucleophosmin* (*NPM*)*1-ALK* translocation t(2;5)(p23;35), which can be further confirmed by fluorescence *in situ* hybridisation.

The student completed his laboratory search for the final diagnosis and returned to the physician-tutor to discuss this unusual and educative case and its management.

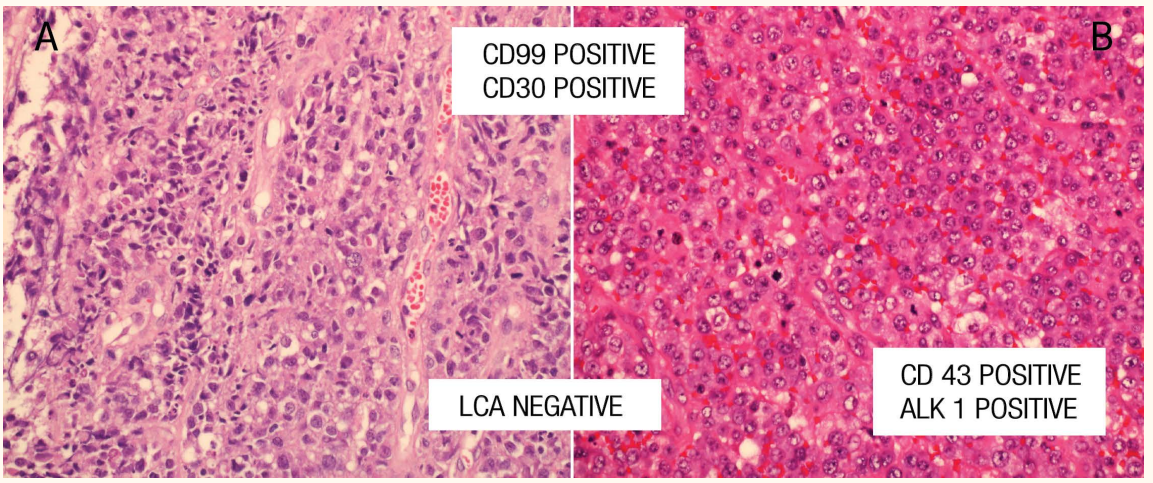

Figure 4A & B: Haematoxylin and eosin stains of biopsies from the (**A**) bronchial mass and (**B**) thigh mass showing a malignant round blue cell tumour at x100 magnification. Boxes display immunohistochemistry patterns in both biopsies: CD99, CD30 positive/LCA negative. Additional markers on the thigh biopsy clinched the diagnosis of anaplastic large cell lymphoma by immunoreactivity for ALK and CD43.

CD = cluster of differentiation; LCA = leukocyte common antigen; ALK = anaplastic lymphoma kinase.

Complexities of 21st Century Cancer Management

After the student had recounted his learning experience, the physician outlined the two questions he should now consider as a medical student. First, in view of the past treatment for thalassaemia major with allogeneic bone marrow transplantation, could the ALCL be regarded as a 'secondary' cancer? Second, what was unique about ALCL which justified the elaborate attempts made to accurately characterise this type of NHL?

Firstly, in 21st century practice of medicine, the success of a cancer cure comes with the downside of diagnosis and the treatment of 'secondary' cancers that arise on a background of immunosuppression. Immunosuppression may be secondary to therapy (chemoradiotherapy or conditioning for BMT) or due to the first malignancy itself, such as haematolymphoid malignancies.[6] The incidence increases with time and is approximately 15% at 15–20 years from the time of the first treatment.[6] Secondary cancers are usually acute non-lymphocytic leukaemia, NHL or solid tumours (especially in the field of radiation). Amongst NHL, the most common sub-type is B-cell lymphoma; if immunosuppression-driven, it is associated with the Epstein-Barr virus. This patient received high doses of alkylating agents as part of the conditioning regimen for BMT and this may well have caused the ALCL.

The second question relates to understanding ALCL; this is one of the several types of mature T/natural killer (NK)-cell lymphomas, accounting for almost a quarter of all the T/NK-cell lymphomas in North America, around 6% of the T cell lymphomas in Asia and 10% of all NHLs in Oman.[7–9] ALCL presents either with cutaneous involvement only (cALCL) or with systemic involvement (sALCL).[10] The significant majority of patients with sALCL have a translocation t(2;5) causing a *NPM-ALK* fusion gene, resulting in an 80 kilodalton protein. An IHC demonstration of this protein is helpful in several ways: in diagnosing difficult cases (as in this patient), defining the prognosis and as a predictive marker for treatment with a specific tyrosine kinase inhibitor (crizotinib).[11] The presence of ALK translocation is an independent favourable prognostic factor. ALK-positive cALCL usually presents in the first three decades of life and, despite the advanced stage at presentation, has a better prognosis (around 75% overall survival at five years).[11] ALK-negative sALCL, on the other hand, usually occurs in the elderly with a poor overall survival rate of less than 25% at five years.[11]

As demonstrated in this patient, ALCL also strongly expresses CD30 antigen, which promotes cell proliferation and survival, upregulates the susceptibility to *apoptosis* signalling and downregulates the immune response. All of these factors make CD30 antigen an attractive target for diagnosis and targeted treatment with brentuximab vedotin (the anti-CD30 antibody).[12] Thus, IHC detection of characteristic molecular alterations provide unprecedented targets for the management of ALCL.

The session concluded with the student acknowledging the unique patient-to-laboratory learning journey he had undertaken through this patient's disease complexities; exhorting his peers in the audience to replicate such learning opportunities in their clinical years and beyond.

Epilogue

The narrative of this patient is evocative of secondary cancers (post-BMT lymphoproliferative disorders), iatrogenic outcomes (infectious predisposition), the challenges of technology (IHC), and cutting-edge personalised medicine (molecular targets in oncologic practice). All of these provide the learning content that the SCRAPS arena aims for. However, in this interactive SCRAPS presentation, one of an infinitesimal number of strategies medical educators can adopt was used to make the clinico-pathological session a simulated exercise in reality.[2] Integrated curricula in leading educational centres have introduced other methods like pathology special study modules or pathology-led problem-based learning to achieve this synthesis.[13] A recent review from the USA recommended the inclusion of the vital competency of 'diagnostic medicine' overseen by the Liaison Committee on Medical Education to fulfil holistic integration of the laboratory with clinical practice.[14] Curricular time in clinical years often precludes allotting additional hours to revisit the laboratories. The concept that assessment drives learning has prompted UK educators to suggest that objective structured clinical examinations in clinical assessment should include pathologists in the design and evaluation process.[15]

A common phenomenon in medical students' learning is emphasis on the concept and neglect of procedural knowledge of laboratory inputs, which can later lead to poor strategising when requesting and interpreting tests.[16] This case presentation brings this issue to the fore and makes a case for finding more opportunities to reinforce laboratory education beyond the didactic curricular hours, perhaps in the format of interprofessional education.[17] Novel medical curricula, including the World Federation for Medical Education-accredited integrated curriculum offered at the COMHS of SQU, abound in innovative strategies for improving the teaching skills of students.[18–20] The SCRAPS forum is one more arena where this can be effectively practiced. The art of problem-solving and the shaping of professional identity is an integral part of development for the budding physician;[21] brain storming and in-depth discussions prior to such presentations identify grey areas in learning for the learner-presenter, the educator and the target audience; the outcome benefits all three.

Grounded in the grim environs of disease and its increasing complexities, learning and teaching can be made mutual and responsive. It can and should achieve a new dimension to the teacher-taught relationship; embed student-peer learning; integrate clinical, basic and diagnostic specialties; and forge presenter-audience dialogue. It is a golden opportunity for the novice medical clerk to embark on a journey of exploration, confidence and communication. This SCRAPS presentation serves to emphasise the significance of the physician-pathologist dialogue where balanced use and interpretation of sophisticated tests and imaginative educational methods extended beyond the curriculum to groom physicians-in-the-making.

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CME Quiz Questions

1. Which of the following is classified as a small round blue cell tumour?

a. Adenocarcinoma
b. Hepatocellular carcinoma
c. Lymphoma
d. Squamous cell carcinoma

2. A specialised histotechnique commonly used in identifying the cell lineage in a poorly differentiated tumour is:

a. Enzyme histochemistry
b. Electron microscopy
c. Immunohistochemistry
d. Mucin histochemistry

3. Which antibody is immunoreactive with the majority of ALCL?

a. ALK-1
b. CD20
c. CD99
d. S-100

4. Which of the following cell lineages do most ALCL belong to?

a. B
b. Dendritic
c. Histiocytic
d. T

5. Which antigen expressed on the ALCL cell also serves as a target for treatment with a therapeutic antibody?

a. Bcl-2
b. CD30
c. CD43
d. CD3

6. Which second malignancy is most common after bone marrow transplantation?

a. Lymphoma/leukaemia
b. Carcinoid
c. Sarcoma
d. Glioma

7. Which one of the following groups of chemotherapy is most often associated with an increased risk of second malignancy?

a. Alkylating agents
b. Antimetabolites
c. Vinca alkaloids
d. Anthracyclines

8. A total of 85% of ALCL patients have a translocation, t(2;5) leading to *NPM-ALK* fusion gene, resulting in the translation of a 80 kilodalton protein. Which one of the following agents is now being used as a targeted agent to treat ALCL?

a. Imatinib
b. Gefitinib
c. Crizotinib
d. Sunitinib

9. Brentuximab vedotin has been approved by the FDA for the treatment of relapsed ALCL. To which class of drugs does brentuximab vedotin belong?

a. Chemoradiotherapy
b. Chemo-immunotherapy
c. Monoclonal antibody
d. Tyrosine kinase inhibitor

10. t(2;5) is present in 85% of ALCL cases. If present, the marker could be used for which of the following purposes? Check all correct answers.

a. Diagnosis
b. Staging
c. Grading
d. Prognosis
e. Predictive marker

ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; Bcl-2 = Bacillus collagen-like antigen 2; CD = cluster of differentiation; NPM = nucleophosmin; FDA = Food and Drug Administration.

Answers: 1: c; 2: c; 3: a; 4: d; 5: b; 6: a; 7: a; 8: c; 9: b; 10: a, d, e.