Original Article

Intraoperative pathology consultation for pulmonary lesions: errors and deferrals

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Abstract: The accuracy rate of frozen section constitutes an important step of quality assessment step in pathology practice. This study aimed to investigate pulmonary lesions that were incorrectly diagnosed or postponed for routine examination by pathologists at frozen section examination; it also aimed to discuss the reasons for difficult diagnoses and the various clues enabling the correct diagnosis to be made when such lesions are encountered. This study retrospectively reviewed the medical data of the thoracic surgery cases that underwent frozen section examination between 2009 and 2014. Frozen section errors and deferrals were identified in 25 cases. Fourteen (56%) lesions were of pulmonary parenchymal origin and 11 (44%) were of pleural origin. The number of cases in which the pathologists postponed the diagnosis without making any approach was 14. Of these, 9 (64%) were benign lesions such as bronchiectasis, fibrosis anthracosis, chronic inflammatory cell infiltration, chronic pleuritis, and mesothelial proliferation. The number of misdiagnosed cases was 11. Of these, 7 (64%) were of pulmonary and 4 (36%) were of pleural origin. Because the examination techniques of each pathology department may differ from one another, the comparative examination of frozen sections and routine sections would aid in becoming familiar with various pathologies and would be beneficial for pathologists in minimizing their diagnostic errors.

Keywords: Frozen section, intraoperative pathology consultation, pulmonary lesion

Introduction

Intraoperative pathology consultation, that is, the frozen section (FS), constitutes an important step in the diagnosis and treatment of many pulmonary lesions. The FS indications in pulmonary pathology are similar to those of other systems: a) determining the adequacy of the sample for diagnosis; b) understanding the nature of the lesion; c) confirming a previous diagnosis made by biopsy or another method; d) determining the spread of the disease and evaluating surgical margins; and e) evaluating lymph nodes [1].

FS is a diagnostic method that may present diagnostic dilemmas for a variety of reasons, particularly for inexperienced pathologists.

A pathologist cannot always necessarily reach a definitive diagnosis but rather may postpone a diagnosis, i.e. the tissue sections may be routinely examined and the diagnosis may only be made once the paraffin blocks have been examined. There is also the possibility of rendering an incorrect diagnosis by FS examination.

This study aimed to investigate pulmonary lesions that were incorrectly diagnosed or postponed for routine examination by pathologists at FS examination; it also aimed to discuss the reasons for difficult diagnoses and the various clues enabling the correct diagnosis to be made when such lesions are encountered.

An informed consent form for the use of pathological specimens for scientific purposes is provided to patients as part of the standard procedure prior to the pathological examination.

Materials and methods

This study retrospectively reviewed the medical data of the thoracic surgery cases that underwent FS examination at Uludag University Faculty of Medicine, Department of Pathology
between 2009 and 2014. Lesions of pulmonary or pleural origin that had been misdiagnosed or that went undiagnosed at FS examination and for which a definitive diagnosis was postponed were included. Mediastinal lesions and hilar/mediastinal lymph nodes were excluded. The FS examinations were performed by separate inexperienced pathologists, although the paraffin section diagnoses were made by pathologists experienced in pulmonary pathology. The cases were divided into 2 groups:

1. The cases in which a diagnosis was postponed until after routine examination.
2. The cases that were misdiagnosed by FS examination.

On purpose FS slides were chosen for this study.

### Results

Frozen section errors and deferrals were identified in 25 cases. Of these 25 cases, 7 (28%) were female and 18 (72%) were male. The overall average age was 59.7 years. Fourteen (56%) lesions were of pulmonary parenchymal origin and 11 (44%) were of pleural origin.

The number of cases in which the pathologists postponed the diagnosis without making any approach was 14. Of these, 9 (64%) were benign lesions such as bronchiectasis, fibrosis, and mesothelial proliferation (Table 1).

The number of misdiagnosed cases was 11. Of these, 7 (64%) were of pulmonary and 4 (36%) were of pleural origin. Tumor necrosis and case-
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Figure 1. Squamous metaplasia of the epithelium in bronchiectasia (Frozen section, hematoxylin & eosin, ×200).

Figure 2. Mucinous BAC, typically an abrupt transition between the tumor cells and the uninvolved alveoli (Frozen section, hematoxylin & eosin, ×200).

Figure 3. Hyalinized necrotic area and surrounding histiocytes (Frozen section, hematoxylin & eosin, ×20).

Discussion

The primary aim of FS examination in pulmonary pathology, as in other systems, is to differentiate between malignant and benign conditions and to evaluate surgical margins. FS examination determines the course of surgery in many cases. Although rare, FS examination may provide an incorrect diagnosis. In some cases, a pathologist defers making the diagnosis until after the examination of the sections obtained from paraffin blocks. Postponing a diagnosis primarily aims to avoid a false-positive diagnosis; however, this approach leads to secondary surgical interventions, and to increased morbidity and costs [2]. This study explored pulmonary or pleural lesions whose diagnoses were incorrect or postponed at FS; it also discusses various helpful clues for diagnosis.

The 25 cases included in this study may be categorized into 5 main groups based on lesions detected by microscopic examination:

1. Certain benign changes in lung parenchyma; for example, bronchiectasis, fibrosis, inflammation, and type II pneumocyte hyperplasia.

2. Differentiation of type II pneumocyte hyperplasia and non-mucinous bronchioalveolar carcinoma (BAC) and adenocarcinoma.

3. Differentiation between malignancies and benign conditions such as pleural mesothelial proliferation and chronic pleuritis.

4. Differentiation between malignant mesothelioma and adenocarcinoma in the pleura.

5. Differentiation between tumor necrosis and granulomatous inflammatory necrosis.

In FS examination of the lung, benign changes should be principally recognized. Our results demonstrated that 9 cases with postponed diagnosis and 6 misdiagnosed cases had benign pulmonary changes. For example, bronchiectasis is not a problematic in routine pathology; however, as our results indicated, it may present challenges at FS examination. In addition to the typical bronchial findings, bronchiectasis may exhibit histological changes made incorrectly in two cases of foreign body reactions (Table 2).
characterized by bronchial epithelial shedding, epithelial squamous metaplasia, and bronchial mural destruction [3]. In cases accompanied by these findings, examination by frozen section may be particularly more confusing. For example, if complete bronchial epithelial shedding is present in a dilated bronchus, it will be visualized as a space lined by inflammatory cells. In this case, a careful scan of the inner lining of the space to identify the remaining bronchial epithelial residua may be helpful (Figure 1). If squamous metaplasia of the epithelium is present, obtaining a few more sections to capture the transition of squamous epithelium to respiratory epithelium may also aid in arriving at a correct diagnosis. Additionally, tangential sections of from bronchiectasis with squamous metaplasia in the epithelium may lead to incorrect conclusions such as epithelial nuclear stratification, nuclear crowding, and hyperchromasia [2].

Our study results indicate that non-mucinous bronchioloveolar carcinoma (BAC) and type II pneumocyte hyperplasia may be confused. By FS, as shown in Table 2, a case diagnosed as fibrosis and type II pneumocyte hyperplasia by permanent sections was diagnosed as BAC by FS. In contrast, a case of BAC was considered as benign by FS. In fact, reactive pneumocyte hyperplasia, atypical adenomatous hyperplasia, and non-mucinous BAC (adenocarcinoma with lepidic pattern according to the new classification) are lesions that may create diagnostic difficulties not only for FS examination, but also with regard to paraffin sections. As a clue, reactive hyperplasia in pneumocytes accompanies another lesion and, for example, in conditions where the alveolar epithelium is damaged, including bronchiectasis, idiopathic pulmonary fibrosis/usual interstitial pneumonia, honeycomb lung, diffuse alveolar injury, and radiation pneumonia, such changes are observed as a component of these lesions. Fibroblastic proliferation and inflammatory infiltration in neighboring alveolar septae are helpful hints for diagnosis. In particular alveolar structures that remain, or are trapped, between fibrotic tissues may be confusing; especially when changes such as reactive hyperplasia occur in the pneumocytes of these alveoli, in which case the lesion may be incorrectly diagnosed as non-mucinous BAC. An important differential diagnostic finding in non-mucinous BAC is that cells with moderate nuclear atypia line the alveolar inner surface and there is no inflammation accompanies the lesion. In addition to marked atypia, a multiple growth pattern, i.e. papillary structures in addition to tubular structures may aid in the diagnosis of adenocarcinoma [2, 4]. In mucinous BAC, typically an abrupt transition between the tumor cells and the uninvolved alveoli may be helpful at frozen section (Figure 2).

The recent advance in radiological techniques has allowed the detection of small solitary pulmonary nodules (SPN). A classical solitary pulmonary nodule is an asymptomatic, round or ovoid shaped lesion with sharp borders, which is surrounded by normal lung tissue. Establishing a correct diagnosis by transbronchial
or transthoracic biopsy may be challenging in some small lung nodules. Most SPNs are excised via a wedge biopsy and the first examination is conducted by frozen sections. A SPN may be a lung carcinoma or a metastatic nodule; however, it should be considered that it might also be a benign lesion, such as a tuberculous granuloma, an intraparenchymal lymph node, or hamartoma [5]. Even when a definitive diagnosis cannot be made, an opinion as to malignant or benign would be helpful in guiding surgery. One should always bear in mind that in regard to FS, the distance of the lesion to surgical borders and the pleura should be recorded. No more than the required number of samples should be removed from a lesion for FS examination. As much tissue should be preserved, as possible, particularly for small lesions. In lesions smaller than 1 cm, one should attempt to make a diagnosis with the help of only one section and part of the lesion should always be fixed in formalin solution for later studies using special dyes.

My personal experience indicates that inflammatory cells may be larger than usual in frozen sections, raising the possibility of a malignant condition, particularly when the cytological features are not easily discernible. In such cases larger-than-normal endothelial cells of the vascular structures accompanying an inflammatory reaction may aid the pathologist in making the diagnosis of an inflammatory reaction and in avoiding a false-positive diagnosis.

A tumoral growth should not be necessarily diagnosed when one solely observes necrosis in the frozen section; necrotizing granulomatous inflammation is also included in the differential diagnosis. It is difficult to differentiate tumor necrosis from a granulomatous reaction is a section consisting solely of necrosis. Visualizing the silhouette of necrotic tumor cells may be of some help; however, it would be still appropriate to obtain a new sample for frozen section and to search for tumor cells or epithelioid histiocytes and Langhans-type giant cells. If hyalinized necrotic areas are observed, attempts an identifying surrounding histiocytes must be made (Figure 3).

One of the reasons of incorrect diagnosis by FS examination is examining a preparation rapidly and over a brief time period. We observed that one case was inappropriately diagnosed as a benign condition despite the presence of a tumor cell group (Figure 4). In another case because foreign bodies were overlooked, a foreign body reaction was evaluated as tumor (Figure 5). As Peters [6] emphasized: “Despite the more urgent setting, we should do our best to avoid rushing through cases requiring lengthy screening and concentration. It is very easy to overlook a small tumor cell cluster on the side of the road if we are driving at high speed”.

Reactive pleural changes and tumoral infiltrations in the pleura are responsible for some of the diagnostic challenges in FS. Eleven of 25 cases were pleural lesions in our study. It is interesting that three of the six pleura cases in which no diagnostic opinion could be offered at FS were diagnosed by permanent sections as malignant mesothelioma (MM) (Table 1). Pleuritis and malignancy could not be differentiated in two cases (Table 2). Mesothelial cells lining the pleural surface exhibit reactive hyperplasia when the pleura are irritated or inflamed. Reactive mesothelial hyperplasia frequently accompanies organized fibrinous pleuritis or fibrous pleuritis. Simple reactive mesothelial hyperplasia is usually not confused with a malignancy, although many fluorid reactive mesothelial hyperplasia cases are characterized by one or more features of cytological atypia reminiscent of malignancy such as increased cellularity, large nuclei, prominent nucleoli, or increased mitoses [4]. An important point for the differentiation of reactive mesothelial proliferation and epithelioid type MM is that in the latter condition, the tumoral cells invade fat tissue, muscle tissue, or lung parenchyma. Reactive mesothelial hyperplasia in response to inflammatory pleural conditions does not have an invasive character, although hyperplastic mesothelial cells in organized serosal inflammatory reactions may be embedded in fibrous tissue. This condition is called “benign mesothelial entrapment” and it should be considered in the differential diagnosis of pleural lesions. A useful clue in these instances would be the presence of a fibrinous or neutrophilic inflammatory reaction [3, 4, 7]. Because epithelioid MM, encompasses many types such as solid, tubulopapillary, acinar, signet ring cell, and clear cell, it is morphologically impossible to differentiate it from lung adenocarcinoma or from metastatic carcinomas to the pleura, and immunohistochemical examination is necessary for a
definitive diagnosis [7]. As shown in Table 2, one of the pleural cases that received an adenocarcinoma diagnosis was later diagnosed as MM on permanent sections. In my personal opinion, tumoral pleural invasion should be designated as “malignant” and the tumor typing should be postponed until after the immunohistochemical examination.

We explored pulmonary lesions that were misdiagnosed and wherein the diagnosis was deferred at FS examination. The accuracy rate of FS constitutes an important step of quality assessment step in pathology practice. A correct diagnosis principally requires good technique followed by a meticulous examination. Because the examination techniques of each pathology department may differ from one another, the comparative examination of frozen sections and routine sections would aid in becoming familiar with various pathologies and would be beneficial for pathologists in minimizing their diagnostic errors.

Disclosure of conflict of interest

None.

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