European Journal of Radiology 85 (2016) 1708–1715

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Thin-section computed tomography–histopathologic comparisons of pulmonary focal interstitial fibrosis, atypical adenomatous hyperplasia, adenocarcinoma in situ, and minimally invasive adenocarcinoma with pure ground-glass opacity

Ming-Jue Si (M.D. PhD.)[a,1], Xiao-Feng Tao (M.D. PhD.)[a,*,1], Guang-Ye Du (M.D.)[b,1], Ling-Ling Cai (M.D.)[a], Hong-Xiu Han (M.D. PhD.)[b], Xi-Zi Liang (M.D.)[b], Jiang-Min Zhao (M.D. PhD.)[a,1]

[a] *Department of Radiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, No. 280, Mohe Road, Shanghai 201999, China*

[b] *Department of Pathology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, No. 280, Mohe Road, Shanghai 201999, China*

ARTICLE INFO

Article history:
Received 24 April 2016
Received in revised form 4 July 2016
Accepted 17 July 2016

Keywords:
Thin-section CT
Pure ground-glass opacity
Focal interstitial fibrosis
Atypical adenomatous hyperplasia
Adenocarcinoma in situ
Minimally invasive adenocarcinoma

ABSTRACT

Objective: To retrospectively compare focal interstitial fibrosis (FIF), atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA) with pure ground-glass opacity (GGO) using thin-section computed tomography (CT).

Materials and methods: Sixty pathologically confirmed cases were reviewed including 7 cases of FIF, 17 of AAH, 23of AIS, and 13 of MIA. All nodules kept pure ground glass appearances before surgical resection and their last time of thin-section CT imaging data before operation were collected. Differences of patient demographics and CT features were compared among these four types of lesions.

Results: FIF occurred more frequently in males and smokers while the others occurred more frequently in female nonsmokers. Nodule size was significant larger in MIA ($P < 0.001$, cut-off value = 7.5 mm). Nodule shape ($P = 0.045$), margin characteristics ($P < 0.001$), the presence of pleural indentation ($P = 0.032$), and vascular ingress ($P < 0.001$) were significant factors that differentiated the 4 groups. A concave margin was only demonstrated in a high proportion of FIF at 85.7% ($P = 0.002$). There were no significant differences (all $P > 0.05$) in age, malignant history, attenuation value, location, and presence of bubble-like lucency.

Conclusion: A nodule size >7.5 mm increases the possibility of MIA. A concave margin could be useful for differentiation of FIF from the other malignant or pre-malignant GGO nodules. The presence of spiculation or pleural indentation may preclude the diagnosis of AAH.

1. Background

With the development and increased use of thin-section computed tomography (CT) in clinical screening for lung cancer or other purposes, small ground-glass opacity (GGO) nodules are encountered with increasing frequency [1]. GGO is a hazy, increased attenuation in the lung that does not obliterate the bronchial or vascular margins, as defined by the Fleischner Society [2,3], and can be further classified as either pure GGO (without a solid component) or mixed GGO (containing both solid and ground-glass components) [4]. Histologically, the common factor in GGO is partial filling of the terminal air spaces, interstitial thickening by fluid, cells, fibrosis, and increased capillary blood volume, or a combination of these factors [5].

A new international classification system for lung adenocarcinoma has been proposed by WHO in 2015 [6]. On thin-section CT, if a lung nodule shows a pure ground glass appearance, this would favor a preinvasive lesion, including atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS), both of which

* Corresponding author.
E-mail addresses: smjsh@hotmail.com (M.-J. Si), taoxiaofeng1963@hotmail.com (X.-F. Tao), 715376158@qq.com (G.-Y. Du), caill_00@163.com (L.-L. Cai), hanhongxiu@hotmail.com (H.-X. Han), liangxizish@hotmail.com (X.-Z. Liang), zhaojiangmin1962@hotmail.com (J.-M. Zhao).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ejrad.2016.07.012
0720-048X/

are defined as small lesions of ≤3 cm demonstrating purely lepidic growth; or possibly minimally invasive adenocarcinoma (MIA), defined as predominantly lepidic lesions measuring ≤3 cm with invasive components measuring no more than 0.5 cm; and less likely lepidic predominant adenocarcinoma [6]. Lepidic predominant invasive adenocarcinoma usually manifests as partly solid GGO nodules (with both GGO and solid components) or solid nodules [6].

Although several articles have reported on CT-pathological comparisons for AAH, AIS and MIA [4,7–9], few reports have indicated how to discriminate preinvasive adenocarcinomas and MIA from focal interstitial fibrosis (FIF), which is also an important constituent of pure GGO lesions. The aim of the present study was to investigate characteristic imaging features on thin-section CT for differential diagnosis among nodules of AAH, AIS, MIA, and FIF presenting with pure GGO, and to compare the results with histopathological data.

2. Materials and methods

Our study was approved by the institutional review board and the requirement for informed consent was waived, given the retrospective nature of the study. Written informed consent was obtained for the use of CT scans from all patients.

2.1. Subjects

We retrospectively reviewed the CT imaging data of 109 pure GGO nodules between January 2010 and December 2015 in our institution. Forty-nine cases were not resected. Of these, 3 cases demonstrated very small size (≤5 mm) on the first CT scan, with no need for follow-up according to the Fleischner Society recommendations [2], while 46 cases with nodule size >5 mm underwent CT follow-up and were not resected before December 2015. These were excluded because of a lack of histopathological confirmation. A total of 60 cases of pure GGO nodules in 59 patients were resected and examined pathologically in our hospital, all of which underwent single or serial thin-section (≤1 mm) CT scans before surgery, and were included in this study. These nodules were initially detected in a variety of clinical situations. Forty-five (75%, 45/60) nodules were incidentally detected on CT during periodic health check-ups, 7 (11.7%, 7/60) were found on CT images of unrelated pulmonary or extra-pulmonary diseases, and 8 (13.3%, 8/60) were found on routine follow-up CT scans for patients with a previous malignant tumor history (5 patients had papillary carcinoma of the thyroid and 3 had adenocarcinoma of the lung). Fifty-five (91.7%, 55/60) cases were resected before the publication of guidelines for managing subsolid pulmonary nodules by the Fleischner Society in 2013 [2]. Of these, 37 cases underwent surgery immediately after the first thin-section CT scan because of the presence of clinical and morphologic risk factors of malignancy (21 cases), or due to patient anxiety or clinician uncertainty (16 cases), while 18 cases underwent surgery after two or more CT follow-up scans and were finally resected with consensus between clinicians and radiologists. Five cases demonstrated an increase in size and/or attenuation during CT follow-up, and were resected according to the Fleischner Society recommendations [2].

2.2. CT image acquisition and evaluation

Chest CT was performed on a 64-detector row scanner (Brilliance 64 slice CT, Philips Medical Systems, Cleveland, OH, USA) using unenhanced spiral acquisitions (tube voltage: 120 kVp; tube current: 130–200 mA; collimations: 0.625 mm; pitch: 0.758–1.015; rotation time: 0.5s; field of view: 350 mm; matrix: 512). Raw data of images were reconstructed at 0.67 mm thickness and 1 mm intervals using an edge-enhanced algorithm for lung parenchyma. Multiplanar reconstruction and three-dimensional volume-rendered images were performed in some of the cases to reveal the morphological features and the relationship with the adjacent bronchi and blood vessels. Enhanced CT was not performed because evaluation of contrast enhancement of GGO nodules with too much air and insufficient solid components can cause misregistration on pre- and post-contrast images leading to inaccurate results [10].

All nodules kept pure ground glass appearance before surgical resection and the last time of CT imaging data before operation were collected and evaluated. Two radiologists with 7 and 19 years of experience in chest CT interpretation assessed the images independently, blinded to the histopathological diagnosis of the GGO nodules, and decisions on CT findings were reached by consensus. All images were reviewed on a workstation for lung parenchyma (window width: 1500 HU; window level: −500 HU) and mediastinum (window width: 400 HU; window level: 40 HU). CT scans were assessed by observing nodule location (upper/middle/lower lobe or inner/peripheral distribution), size, attenuation value, and morphological characteristics, including shape (classified as "round or oval" and "polygonal or irregular"), margin (classified as "smooth", "slightly lobulated" or "lobulated and spiculated", and "convex" or "concave"), the presence of air bronchogram, bubble-like lucency, pleural indentation, and pulmonary vascular ingress into the lesion (Fig. 1).

Nodules were considered peripherally distributed if they were located in the lateral two-thirds of the lung parenchyma on axial CT image. Both nodule size and CT attenuation values were measured on the axial edge-enhanced series. Nodule size was defined as the maximal diameter on the axial lung window image on the latest thin-section CT scan before surgery [11,12] (Fig. 1). CT attenuation values were measured on the latest unenhanced thin-section CT before surgery using region-of-interest (ROI) cursors, which were drown manually and covered two-thirds of the largest area in a GGO nodule away from air space [4]. The average values of the nodule size and CT attenuation values obtained by the 2 radiologists were used for statistical analysis. Shapes that were not round or oval were considered polygonal or irregular. A lobulated margin was defined when a portion of the lesion's surface showed a wavy or scalloped configuration. A spiculated margin was defined as the presence of strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface. A convex margin reflected an expansive growth pattern, and a concave margin reflected a contracted appearance. An air bronchogram was considered present when air-filled bronchi were present in the lesion. A bubble-like lucency was defined as round or ovoid air attenuation within the nodule [3,13]. A pleural indentation was defined as a linear attenuation leading from the nodule toward the pleura or the major or minor fissure [4,8].

2.3. Histopathological evaluation

For each case, the surgical specimens were reviewed and classified according to the newest 2015 WHO Classification criteria for lung adenocarcinoma as AAH, AIS, and MIA [5]. FIF was histologically defined as interstitial septal thickening with fibroblast proliferation and preservation of the intra-alveolar air space [14]. In addition, vascular, lymphatic, and pleural invasion was also evaluated for AIS and MIA.

2.4. Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0; Chicago, IL). A P-value less than 0.05 was considered statistically significant.