Eur Radiol (2007) 17: 2325–2331
DOI 10.1007/s00330-007-0596-z

Chang Min Park
Jin Mo Goo
Hyun Ju Lee
Chang Hyun Lee
Doo Hyun Chung
Eun Ju Chun
Jung-Gi Im

Focal interstitial fibrosis manifesting as nodular ground-glass opacity: thin-section CT findings

Received: 16 July 2006
Revised: 17 January 2007
Accepted: 18 January 2007
Published online: 14 February 2007

C. M. Park · J. M. Goo · H. J. Lee · C. H. Lee · E. J. Chun · J.-G. Im
Department of Radiology,
Seoul National University College of Medicine, and Institute of Radiation Medicine, Seoul National University Medical Research Center,
Seoul, South Korea

D. H. Chung
Department of Pathology,
Seoul National University College of Medicine,
Seoul, South Korea

J. M. Goo (✉)
Department of Radiology,
Seoul National University Hospital,
28 Yeongeon-dong, Jongno-gu,
Seoul, 110-744, South Korea
e-mail: jmgoo@plaza.snu.ac.kr
Tel.: +82-2-20722624
Fax: +82-2-7477418

Abstract The purpose of this study was to describe the thin-section computed tomographic (CT) features of focal interstitial fibrosis manifesting as nodular ground-glass opacity (GGO) and its changes during follow-up. The thin-section CT findings of pathologically proven focal interstitial fibrosis manifesting as nodular GGO were retrospectively evaluated in nine patients (five women and four men; mean age, 59.3 years; age range, 34–81 years). The thin-section CT findings of each lesion were analyzed for multiplicity, location, shape, margin characteristics, pleural retraction or vascular convergence, size and internal attenuation, lesion internal features and lesion changes on follow-up CT scans (mean 90 days, range 5 to 215 days). All lesions manifested as a solitary nodular GGO (100%), and seven of the nine lesions (77.8%) were located in the upper lobe. Focal interstitial fibrosis was round or oval in shape in five cases (55.6%), complex in shape in three cases (33.3%) and polygonal in one case (11.1%). Lesion margins were smooth in five patients (55.6%), irregular in three (33.3%) and spiculated in one (11.1%). Pleural retraction or vascular convergence was present in two patients (22.2%). Lesions measured 4.8 mm to 25.5 mm (mean, 11.5 mm) and had attenuations ranging from −151 to −699 HU (mean, −514.7 HU). Eight (88.9%) manifested as pure nodular GGOs and one as mixed GGO with a spiculated margin. In all patients, no lesion changes were observed in follow-up CT scans. Focal interstitial fibrosis manifesting as nodular GGO usually presents as a solitary nodule with pure GGO on thin-section CT, which does not change significantly during follow-up.

Keywords Lung · CT · Ground-glass opacity · Fibrosis

Introduction

The widespread use of CT for lung cancer screening and technologic advances now allow many faint peripheral lung nodules to be detected [1]. Focal ground-glass opacity (GGO) with a nodular configuration or nodular GGO is a common CT finding [2].

Nodular GGO is a non-specific finding that may be caused by various disorders, such as eosinophilic pneumonia, focal hemorrhage, focal organizing pneumonia, focal interstitial fibrosis and neoplastic diseases [3]. However, several authors have strongly suggested that nodular GGO represents a precancerous lesion like atypical adenomatous hyperplasia or early lung cancer, e.g., bronchioloalveolar carcinoma or early adenocarcinoma [4–8]. Observation over several months is often helpful in differentiating benign conditions from malignancies and precancerous lesions, because the appearance of most benign nodular GGO lesions, such as focal inflammation, hemorrhage and edema, can easily change over a short period of time [3, 4]. However, focal interstitial fibrosis frequently shows little change even over a considerable period of time in spite of its benign histology. Therefore, it is extremely difficult to differentiate focal interstitial

fibrosis from neoplastic nodular GGOs during follow-up and on initial images, even on thin-section CT [2, 4, 7–11].

Few reports provide a comprehensive assessment of focal interstitial fibrosis including its radiologic and pathologic features. Thus, the purpose of this study was to describe the thin-section CT features of focal interstitial fibrosis manifesting as nodular GGO and its changes during follow-up.

Materials and methods

Patients

From September 2002 to October 2005, nodular GGOs of 3 cm or smaller were found on the chest CT images of 96 individuals, and follow-up thin-section CTs (1–2.5 mm) were performed in 67 individuals. Forty-three nodular GGOs in 35 individuals were pathologically confirmed by lobectomy (n=30), wedge resection (n=12) or cutting needle biopsy (n=1). Focal interstitial fibrosis was pathologically diagnosed in nine patients (five women and four men; mean age, 59.3 years; age range, 34–81 years), and this study was conducted retrospectively. The electronic medical records of these individuals were reviewed, and their clinical features are summarized in Table 1. All patients were treated by standard thoracotomy by lobectomy (n=2), segmentectomy (n=1) or wedge resection (n=6). Five patients were never-smokers and four were current smokers. All were asymptomatic. The lesions were detected by CT for lung cancer screening in seven asymptomatic individuals and by metastasis work-up CT in two. One patient had a history of tuberculosis pleuritis and one patient a history of malignant peripheral nerve sheath tumor in the axilla. One patient had a family history of lung cancer and concurrent bronchioloalveolar carcinoma in the lung, and one had a concurrent thymic carcinoma. Intervals between lesion detection and surgery ranged from 35 to 240 days with a mean of 107.3 days.

CT scanning

CT scanning was obtained at end inspiration. One patient (patient 4) had thin-section CT initially, and the remaining patients (n=8) had an initial thick-section CT. All patients (n=9) had follow-up thin-section CTs, and patients underwent chest CT examinations at an average of 2.7 times (ranging from two to four times) before surgery. The mean CT follow-up period was 90 days with a range of 5 to 215 days.

CT scanning was performed using various CT scanners, namely, LightSpeed Ultra, HiSpeed Advantage (GE Medical Systems, Milwaukee, WI); Sensation-16, Somatom plus 4 (Siemens Medical Systems, Erlangen, Germany); MX-8000 (Phillips Medical Systems, the Netherlands). CT was performed at 120 kVp, 200–400 mA, and at a pitch of 0.875–1.5. Images were reconstructed using high-frequency algorithms with a 1–8-mm slice thickness. Thin-section CT images were designated as being 1–1.25 mm in slice thickness, and thick-section images indicated CT images 5 mm or thicker in slice thickness.

Evaluation of CT features

Four radiologists (C.M.P., H.J.L., C.H.L. and J.M.G.) analyzed all CT images including thin-section CT, with a lung setting of: window level, −700 HU, and width, 1,500 HU, retrospectively, and discrepant results were resolved by consensus. The thin-section CT findings of each lesion were analyzed as follows: (1) multiplicity, (2) location, (3) shape (round or oval, polygonal, complex), (4) margin (smooth, irregular, spiculated; well-defined, ill-defined), (5) pleural retraction or vascular convergence, (6) size and internal attenuation and (7) internal features (pure GGO, mixed GGO or solid).

When comparing follow-up and initial CTs, we paid great attentions to any lesion change, e.g., shape, marginal characteristics, vascular convergence, size and internal attenuation, and solid component appearance. The readers conducted this analysis with two image sets displayed side by side on an LCD monitor.

One radiologist (C.M.P.) recorded the size and internal attenuation (HU) at the largest section of a lesion and carefully placed a region of interest on the whole lesion. These measurements were performed in triplicate, and mean values were recorded. Lesion size was defined as the average product of the height and width of a lesion.

The term ‘polygonal shape’ is used to describe a lesion with linear or concave margins at every corner, and ‘complex shape’ is used to describe all shapes other than those described as round, oval or polygonal. A spiculated margin was defined as one with at least one linear density projecting into the surrounding parenchyma and a well-defined margin as a distinct interface between a lesion and the surrounding parenchyma at more than 50% of the imaged circumference. Vascular convergence was deemed present if vasculature crowding was evident within a nodule or vessels around a lesion converged toward the lesion. Pure GGO indicated GGO without any solid component, and mixed GGO indicated GGO with a solid component.

Histologic evaluations were conducted by conventional hematoxylin and eosin (H&E) staining by an experienced pathologist (D.H.C.), and the histologic sections of resected lesions were compared with corresponding CT images. These comparisons were carried out by consensus between a pathologist (D.H.C.) and two radiologists (J.M.G., H.J.L).

Table 1 Clinical and CT features in nine patients with focal interstitial fibrosis manifesting as nodular GGO in the lung

Patient no./sex/age	Past history of other disease	Concurrent disease in the lung	Time interval from CT to surgery (day)	Thin-section CT findings of focal interstitial fibrosis							Origin of pathologic specimen
				No. of lesion	Location	Shape/margin/ border	Size (mm)	Internal characteristic	Pleural retraction	Internal attenuation (HU)	
1/M/61 Smoker/ 40 PY	TB pleurisy	–	240	1	RUL	Round/ smooth/ well-defined	25.5	Pure GGO	–	−601	RUL lobectomy
2/F/36 Non smoker	–	BAC/RLL/ T1N0M0	114	1	RML	Round/ smooth/ well-defined	5.1	Pure GGO	–	−581	RML wedge resection
3/F/34 Smoker/1.5PY	–	–	69	1	RUL	Round/ smooth/ well-defined	8.5	Pure GGO	–	−477	RUL wedge resection
4/F/50 Non smoker	Malignant nerve sheath tumor (axilla)	–	96	1	LUL	Complex/ spiculated/ well-defined	4.8	Mixed GGO	+	−151	LUL wedge resection
5/M/69 Non smoker	–	–	150	1	LUL	Round./ smooth/ ill-defined	9.3	Pure GGO	–	−552	LLL wedge resection
6/F/40 Non smoker	–	–	36	1	LLL	Complex/ irregular/ ill-defined	20.7	Pure GGO	–	−645	LLL lobectomy
7/M/66 Smoker/40 PY	–	–	35	1	RUL	Polygonal/ irregular/ ill-defined	17	Pure GGO	+	−699	RUL segmentectomy
8/F/47 Non smoker	–	–	163	1	LUL	Round/ smooth/ well-defined	8	Pure GGO	–	−338	LUL wedge resection
9/M/81 Smoker/40 PY	–	Thymic carcinoma	63	1	RUL	Complex/ irregular/ ill-defined	5	Pure GGO	–	−588	RUL wedge resection

No. = number, PY = pack years, TB = tuberculosis, round. = round or oval, GGO = ground-glass opacity, BAC = bronchioloalveolar carcinoma, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe

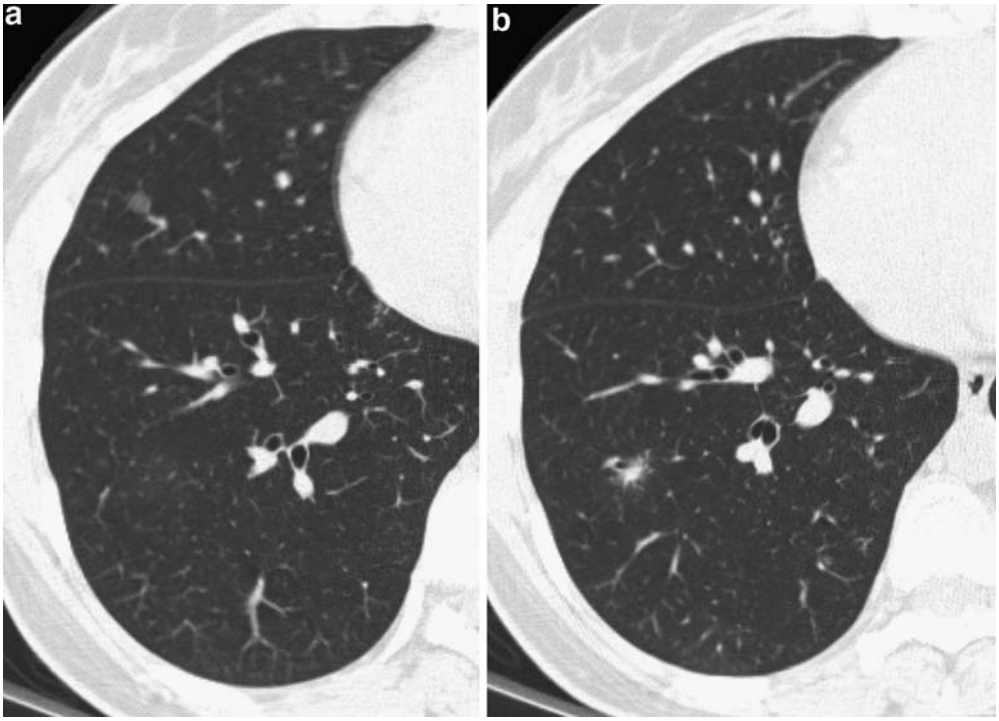

Fig. 1 A 36-year-old woman with two nodular GGOs, of which one was focal interstitial fibrosis and the other was bronchioloalveolar carcinoma. **a** Transverse thin-section CT scan shows a 5.1-mm well-defined round pure GGO nodule in the right middle lobe. This lesion was pathologically confirmed as focal interstitial fibrosis. **b** The other 9-mm mixed GGO nodule containing a central solid portion is shown in the right lower lobe. This lesion was confirmed as bronchioloalveolar carcinoma

Results

Thin-section CT findings in the nine patients with focal interstitial fibrosis manifesting as nodular GGO are summarized in Table 1.

Eight patients had a solitary nodular GGO, and one had two nodular GGOs. In the patient with two lesions, one was of focal interstitial fibrosis and the other of bronchioloalveolar carcinoma (Fig. 1). All lesions of focal interstitial fibrosis in our study manifested as a solitary nodular GGO (100%), and seven lesions (77.8%) were located in upper lobes. Focal interstitial fibrosis appeared round or oval in shape in five cases (55.6%), complex in three cases (33.3%) and polygonal in one case (11.1%) (Fig. 2). Lesion margins were smooth in five patients (55.6%), irregular in three (33.3%) and spiculated in one patient (11.1%). Pleural retraction or vascular convergence was present in two patients (22.2%). Lesions measured from 4.8 to 25.5 mm (mean, 11.5 mm), and lesion attenuation ranged from −151 to −699 HU (mean, −514.7 HU). Eight (88.9%) appeared as pure GGO and one as mixed GGO with a spiculated margin. In patient 4, the lesion showed mixed GGO and a well-defined spiculated margin with pleural retraction, which was resected under the impression of primary lung cancer (Fig. 3). In patient 7, the lesion was polygonal with an ill-defined and irregular margin, and

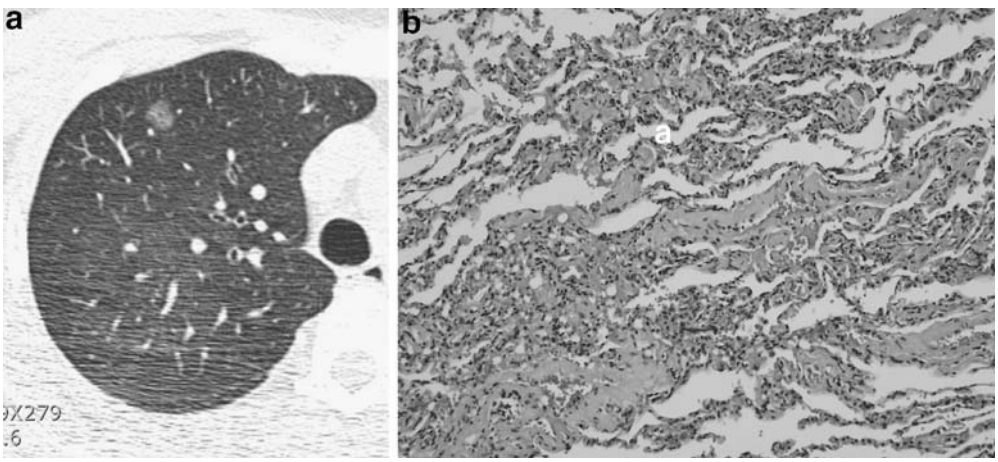

Fig. 2 A 34-year-old woman with focal interstitial fibrosis showing a round pure GGO lesion with a well-defined smooth margin. **a** Transverse thin-section CT scan shows an 8.5-mm well-defined round nodule with pure GGO in the right upper lobe. There was no evidence of spiculation or vascular convergence around the lesion. **b** Photomicrograph of a right upper lobe wedge resection specimen (H&E stained, ×40) shows alveolar interstitial thickening with fibrosis and type II pneumocyte proliferation

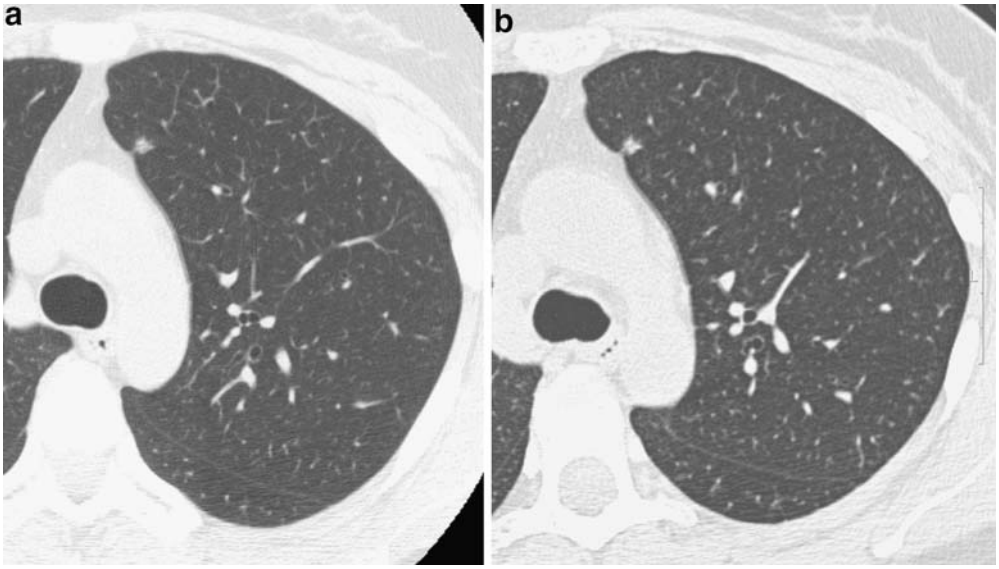

Fig. 3 A 50-year-old woman with focal interstitial fibrosis appearing as mixed GGO with a spiculated margin and pleural traction. **a** Transverse thin-section CT scan shows a mixed GGO nodule in the left upper lobe. Note the spiculated margin and pleural retraction. **b** This follow-up thin-section CT taken 2 months later shows a similar appearance. The lesion was resected under the impression of primary lung cancer. The pathologic diagnosis was of focal interstitial fibrosis without evidence of malignancy

peri-lobular linear opacities were observed around it (Fig. 4). On follow-up CT scans, none of the lesions showed any change in shape, size, marginal characteristics, internal features or vascular convergence in any individual.

The main histologic features of the lesions were focal interstitial thickening with collagen fiber deposition and type-II pneumocyte proliferation and macrophage collection in the airspace.

Discussion

Focal interstitial fibrosis is a focal non-specific pulmonary tissue response to injury, i.e., infection, radiation injury, drug-induced injury, physical pressure, neoplasms, non-specific scars and others [12, 13]. In the present study, all patients were asymptomatic, and lesions were detected incidentally. In addition, all patients had a solitary lesion of focal interstitial fibrosis, which is consistent with other reports [7, 9]. Several investigators [4, 7, 9, 10, 14] have reported in their studies with small numbers of cases that the thin-section CT findings of focal interstitial fibrosis may manifest as nodular GGO. Hara et al. [9] described a lesion that was visualized as a sharply defined pure GGO oval nodule, and Nakajima et al. [7] reported that focal interstitial fibrosis appeared as a pure nodular GGO without spiculation or pleural indentation. Nambu et al. [14] also reported that two of three cases of focal fibrosis showed a well-demarcated pure GGO nodule, whereas the remaining case showed mixed nodular GGO. However, other authors found that lesions had a mixed GGO with indistinct or irregularly deformed margin (n=3) or appeared as solid nodules (n=1) [4]. In the present study, we found that the internal attenuation, margin and shape of focal fibrosis demonstrated a degree of diversity that could include the results of previous studies. One of our cases

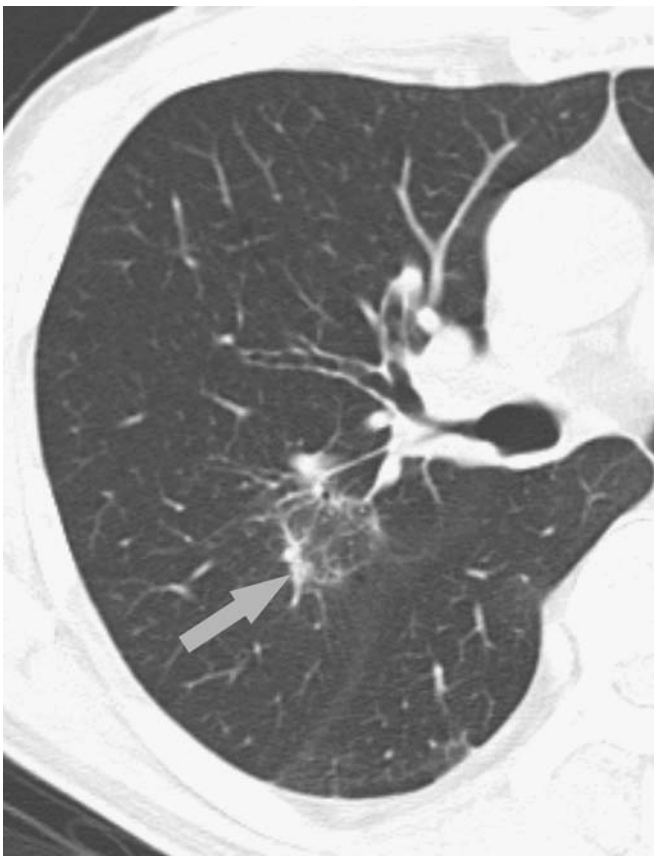

Fig. 4 A 66-year-old man with focal interstitial fibrosis with a polygonal shape and peri-lobular linear density. Transverse thin-section CT scan shows a nodular GGO lesion with peri-lobular linear opacities (arrow) around the lesion in the right upper lobe. Note the pleural traction around the lesion

showed a polygonal shape, which has also been reported by Li et al. [10]. Some investigators have suggested that this finding might be specific for non-neoplastic lesions, including focal interstitial fibrosis [14]. In addition, recent studies have suggested that computerized schemes might help in the detection and analysis of these nodular GGOs [15, 16]. Nevertheless, focal interstitial fibrosis has a lot of common CT features with neoplastic diseases with lepidic growth pattern, and the differentiation between them is often very difficult. Further study with more cases is necessary to evaluate the differential points between focal interstitial fibrosis and neoplasm with lepidic growth.

Theoretically, the morphology of focal interstitial fibrosis could be affected by the progression of the contraction process [10]. However, seven cases (77.8%) in the present study did not show evidence of such contraction processes, e.g., vascular convergence or pleural retraction. The CT findings of focal interstitial fibrosis might be related to the size and maturation of the fibrosis. In the present study, mean lesion size was 11.5 mm and mean attenuation was −514.7 HU, whereas lesions were <10 mm with a mean internal attenuation of −375 HU in the previously mentioned study [10].

In one patient, we observed peri-lobular linear density that consisted of polygonal opacities. This finding has been reported in some cases of organizing pneumonia [17] and histologically is attributed to the accumulation of intraluminal fibroblastic plaque in peri-lobular alveoli [18]. Although every focal interstitial fibrosis does not show this finding, focal interstitial fibrosis may be differentiated from malignancies showing nodular GGO, if this lesion is accompanied with peri-lobular linear density.

In contrast with Li et al.'s study [10], none of our cases changed in appearance, including the shape and marginal characteristics. Moreover, none showed solid component formation or vascular convergence around the lesion on follow-up CT scans. This may have been due to a short follow-up duration between initial and final CT scans in the present study, and thus further study is necessary in a larger number of patients to establish the natural course of this lesion.

The main histological findings of focal fibrosis included fibrotic thickening of alveolar walls associated with collagen fiber deposition, anthracosis and peri-bronchovascular interstitial thickening [10], and we also observed similar features microscopically. The GGO of focal interstitial fibrosis could be representative of such interstitial thickening and partial air space filling by macrophages.

Some limitations of the present study deserve mention. First, there may have been a selection bias. Our study included only histologically proven cases with surgically resected specimens, which may, in itself, have resulted in the selection of cases with CT features similar to lung cancer. Second, focal interstitial fibrosis might manifest as a solid nodule and as a nodular GGO in CT scans, as mentioned above [4]. However, it is important that the detailed CT feature of focal interstitial fibrosis manifesting as nodular GGO be determined, because a nodular GGO lesion, especially when it is persistent, could be a primary lung cancer or precancerous lesion. Moreover, a detailed knowledge of this lesion could be helpful for the differentiation of this disease from neoplastic disease, and thus, for the prevention of unnecessary surgery. Third, the present study was performed retrospectively, a limited number of CT scans were obtained in a small number of patients using various CT scanners and different parameters, follow-up studies were performed with different time intervals, and initial thick-section CT and follow-up thin-section CT studies were carried out on only the majority of patients, which might have hindered an exact evaluation of lesion changes during follow-up. Fourth, follow-up periods were relatively short in terms of identifying natural lesion change. Thus, further study is necessary in a larger number of patients using a more detailed form of analysis. However, given the above shortcomings, we are of the opinion that the present study provides useful information about focal interstitial fibrosis manifesting as nodular GGO.

The present study suggests that focal interstitial fibrosis manifesting as nodular GGO usually appears as a solitary nodule with pure GGO on thin-section CT and that it does not change significantly during follow-up.

References

1. Sone S, Takashima S, Li F et al (1998) Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 351:1242–1245
2. Lee HJ, Goo JM, Lee CH, Yoo CG, Kim YT, Im JG (2007) Nodular ground-glass opacities on thin-section CT: size change during follow-up and pathological results. Korean J Radiol 8:22–31
3. Collins J, Stern EJ (1997) Ground-glass opacity at CT: the ABCs. Am J Roentgenol 169:355–367
4. Takashima S, Sone S, Li F, Maruyama Y, Hasegawa M, Kadoya M (2003) Small solitary pulmonary nodules (< or =1 cm) detected at population-based CT screening for lung cancer: Reliable high-resolution CT features of benign lesions. Am J Roentgenol 180:955–964

5. Park CM, Goo JM, Lee HJ et al (2006) CT findings of atypical adenomatous hyperplasia in the lung. Korean J Radiol 7:80–86
6. Nakata M, Saeki H, Takata I et al (2002) Focal ground-glass opacity detected by low-dose helical CT. Chest 121:1464–1467
7. Nakajima R, Yokose T, Kakinuma R, Nagai K, Nishiwaki Y, Ochiai A (2002) Localized pure ground-glass opacity on high-resolution CT: histologic characteristics. J Comput Assist Tomogr 26:323–329
8. Li F, Sone S, Abe H, Macmahon H, Doi K (2004) Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. Radiology 233:793–798
9. Hara M, Oda K, Ogino H et al (2002) Focal fibrosis as a cause of localized ground glass attenuation (GGA)-CT and MR findings. Radiat Med 20:93–95
10. Li F, Sone S, Maruyama Y et al (2000) Correlation between high-resolution computed tomographic, magnetic resonance and pathological findings in cases with non-cancerous but suspicious lung nodules. Eur Radiol 10:1782–1791
11. Yoshida J, Nagai K, Yokose T et al (2005) Limited resection trial for pulmonary ground-glass opacity nodules: fifty-case experience. J Thorac Cardiovasc Surg 129:991–996
12. Smith DM, Smith SK (1988) The fibrogenic response of adult rat lung to continuous propranolol treatment. Histol Histopathol 3:291–299
13. Otake S, Takahashi M, Ishigaki T (2002) Focal pulmonary interstitial opacities adjacent to thoracic spine osteophytes. Am J Roentgenol 179:893–896
14. Nambu A, Araki T, Taguchi Y et al (2005) Focal area of ground-glass opacity and ground-glass opacity predominance on thin-section CT: discrimination between neoplastic and non-neoplastic lesions. Clin Radiol 60:1006–1017
15. Kim KG, Goo JM, Kim JH et al (2005) Computer-aided diagnosis of localized ground-glass opacity in the lung at CT: initial experience. Radiology 237:657–661
16. Nagao M, Murase K, Yasuhara Y et al (2002) Measurement of localized ground-glass attenuation on thin-section computed tomography images: correlation with the progression of bronchioloalveolar carcinoma of the lung. Invest Radiol 37:692–697
17. Ujita M, Renzoni EA, Veeraraghavan S, Wells AU, Hansell DM (2004) Organizing pneumonia: perilobular pattern at thin-section CT. Radiology 232:757–761
18. Johkoh T, Muller NL, Ichikado K, Nakamura H, Itoh H, Nagareda T (1999) Perilobular pulmonary opacities: high-resolution CT findings and pathologic correlation. J Thorac Imaging 14:172–177