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Review

Isolated Diffuse Ground-Glass Opacity in Thoracic CT: Causes and Clinical Presentations

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Ground-glass opacity (GGO) is defined as increased attenuation of the lung parenchyma without obscuration of the pulmonary vascular markings on CT images. This was originally described with reference to thin-section (high-resolution) CT with collimations of approximately 1 mm. However, GGO also may be evident on thicker-section images and will have a similar meaning. GGO may be the result of a wide variety of interstitial and alveolar diseases and frequently represents a nonspecific finding [1, 2]. GGOs often will be present in the company of other interstitial or alveolar findings on CT. As an alveolar finding, GGO represents partially filled alveoli and often is found at the margins of the consolidated lung. With interstitial diseases, it has been associated with active inflammation in some cases [3–8]. In other situations, GGO adjacent to interstitial abnormalities represents fine fibrosis, below the resolution of CT images. Therefore, if all causes of GGOs are grouped together, there is an impossibly broad differential generated, which includes a large number of interstitial diseases and a large array of alveolar diseases. However, the number of diseases that cause diffuse GGOs in isolation or as the predominant finding, is relatively small and easily can be prioritized with simple clinical information. By isolated, we mean patients who show only GGOs without other interstitial or alveolar findings. By diffuse, we mean patients with GGO that involves the majority of both lungs.

Objective

We have chosen to emphasize clinical information as the best means of narrowing the differential diagnosis of patients with isolated diffuse GGO (ID-GGO) because there is substantial overlap in the appearance of ID-GGO among the various etiologies. Thus, in our experience, the various subtypes of GGO—for example, centrilobular nodules and mosaic attenuation—are not able to be discriminated among the causes of ID-GGO [9].

Four large categories of diseases may produce ID-GGO: diffuse pneumonias, primarily opportunistic infections; some chronic interstitial diseases; acute alveolar diseases; and a group of unusual miscellaneous disorders [9]. Table 1 lists the most common causes of ID-GGO.

There are five clinical scenarios in which ID-GGO is most often encountered: patients who are immunocompromised, patients who are receiving bone marrow–suppressing medications, outpatients who have slowly progressive dyspnea, inpatients and outpatients who have acutely developing dyspnea, and inpatients who are acutely ill. We will review these clinical scenarios and the etiologies most commonly encountered with each scenario.

Immunocompromised Patients

In scenario one, an immunocompromised patient presents with dyspnea and often fever. Patients included in this category are HIV-positive individuals, patients who have undergone organ transplantation, and patients who have received high-dose corticosteroids. In this scenario, the opportunistic infections that cause ID-GGO form the primary differential diagnosis.

Infections Appearing as ID-GGO

Diffuse infections, particularly *Pneumocystis carinii* pneumonia (PCP), are among the most common causes of ID-GGOs. In a series of pathologically proven causes of ID-GGO, the most common causes were a variety of diffuse pneumonias, which accounted for 38% (12 of 32) of cases [9]. Most of these infections are opportunistic and should be among the first entities to consider when ID-GGO is the dominant finding on a CT scan of an immunocompromised host.

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TABLE 1 Causes of Isolated Diffuse Ground-Glass Opacity

Categories	Types of Diseases and Infections
Opportunistic infections	Pneumocystis pneumonia (PCP) Cytomegalovirus pneumonia (CMV) Herpes simplex virus pneumonia (HSV) Respiratory syncytial virus bronchiolitis Other
Chronic interstitial diseases	Hypersensitivity pneumonitis (HP) Desquamative interstitial pneumonia (DIP) Respiratory bronchiolitis interstitial lung disease (RBILD) Nonspecific interstitial pneumonia (NSIP) Acute interstitial pneumonia (AIP) Lymphocytic interstitial pneumonia (LIP) Sarcoidosis
Acute alveolar diseases	Pulmonary edema Heart disease Adult respiratory distress syndrome (ARDS) Other Diffuse alveolar hemorrhage
Other causes	Drug toxicity Pulmonary alveolar proteinosis (PAP) Bronchiolitis obliterans with organizing pneumonia (BOOP, COP) Bronchoalveolar carcinoma

Pneumocystis carinii pneumonia.—PCP is a globally distributed saprophytic fungus [10]. Patients with AIDS and other causes of immunosuppression, such as organ transplant recipients, patients with lymphoproliferative disorders, and patients on high-dose corticosteroids are predisposed to this opportunistic infection [11, 12]. Despite dramatic declines in the incidence of PCP in HIV-infected patients as a result of highly active antiretroviral therapy (HAART) and PCP prophylaxis, PCP remains the most common opportunistic infection in this population [11, 13, 14]. PCP most commonly occurs in the 4th to 6th month following transplantation and may have up to a 47% mortality rate [15, 16]. A history of high-dose corticosteroid administration, cancer chemotherapy, or a hematologic malignancy also may predispose a patient to PCP infection [11, 14].

Patients characteristically will present with fever, nonproductive cough, and dyspnea [17]. Marked hypoxemia also is characteristic of PCP. In those patients who have received corticosteroids, a characteristic presentation of PCP is the occurrence of fever, dyspnea, and ID-GGO toward the end of the steroid taper. Survival with modern therapy has improved dramatically in patients with HIV and now approaches 90%. However, PCP continues to have an ominous prognosis in other patients, with a 30–60% mortality rate [11].

ID-GGOs, either uniformly distributed or in a mosaic pattern, are the most common manifestations of PCP on CT scans [18] (Fig. 1). In HIV-positive patients, this appearance is so characteristic of PCP that some physicians argue that it is pathognomonic of PCP and no further testing is necessary. With more severe disease, GGO may progress to consolidation. The CT appearance of PCP rarely may take a variety of more unusual patterns including upper-lobe-predominant disease, focal areas of consolidation, nodules, and thin-walled cavities [18–22].

Cytomegalovirus pneumonia.—Cytomegalovirus (CMV) is a DNA virus of the herpes group and like other herpes viruses, it can remain dormant within a host cell for years and be reactivated when host immune defenses are depressed. CMV may be an important pathogen in immunocompromised patients such as HIV-positive patients and in patients who have undergone organ transplantation [12]. The majority of adults have been exposed to CMV and, as a result, CMV infection usually is a reactivation of dormant foci. In patients receiving organ transplants, the timing of immunosuppression is well defined, corresponding to the date of transplantation. Thus, the timing of CMV reactivation also is well defined and most often occurs 1 to 6 months following transplantation [23]. CMV infection in HIV-positive individuals has declined dramatically with the institution of HAART [24]. However, the occurrence of CMV disease in patients with AIDS is associated with greater levels of immunosuppression and greater mortality rates than in the general HIV-positive population [25].

Many patients in whom CMV can be detected in blood, urine, and respiratory secretions clinically will be asymptomatic. In patients with clinical symptoms, fever, cough, dyspnea, tachypnea, and an increased alveolar-arterial gradient (Aa gradient) most often will be the presenting symptoms [26].

Many patients with CMV viremia will have normal imaging studies. However, in those with imaging findings, CMV pneumonia usually will appear as ID-GGO on CT scans [23, 26, 27] (Fig. 2). In some cases, small (< 5 mm) nodules may be detected and in more severe cases, diffuse consolidation may be present.

P. carinii and CMV pneumonias affect similar populations, often have similar imaging characteristics, and often cannot be distinguished on the basis of imaging. In general, PCP is more common; however, in certain select settings or situations, such as during the first months after organ transplantation, CMV is a frequent cause of ID-GGO [23, 26, 27].

Herpes simplex virus.—Herpes viruses are a type of DNA virus, which may remain dormant within host cells and reactivate at times of reduced host immunity. A large percentage of the adult population is infected with herpes simplex virus (HSV), which in most cases produces no clinical symptoms [28]. HSV pneumonia is a rare event and most commonly is seen in immunocompromised patients such as organ transplant recipients, patients with AIDS, patients with severe burns, and patients with malignancies [29–32].

Because it represents a reactivation infection, herpes simplex pneumonia characteristically will occur in the first few months following organ transplantation [33, 34]. Patients usually will have oral or genital ulcers before the onset of pulmonary symptoms. Dyspnea, cough, and fever herald the onset of pneumonia.

Herpes pneumonias may appear as ID-GGO, widespread consolidation, or a combination of both on chest radiographs and CT scans [35, 36]. Rarely, only GGO will be present [35]. Associated small pleural effusions commonly are found both by CT and chest radiographs [35].

Respiratory syncytial virus.—Respiratory syncytial virus (RSV) is a common cause of bronchiolitis and pneumonia in children and adults. Infection is most likely to occur in the

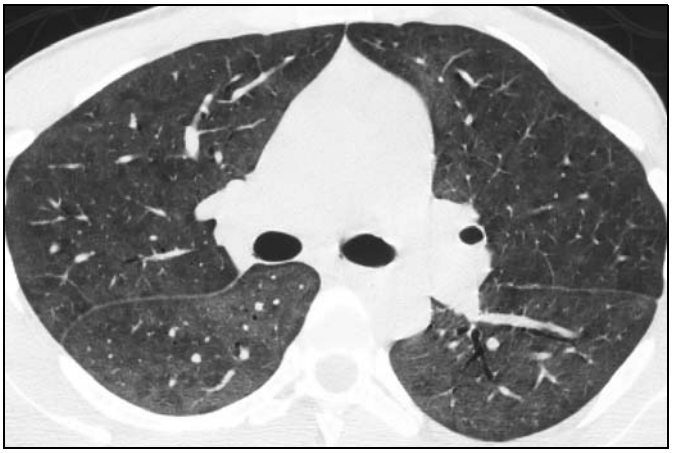

Fig. 1.—29-year-old HIV-positive man with *Pneumocystis carinii* pneumonia. High-resolution CT image through carina shows widespread ground-glass opacity uniformly distributed across lungs.

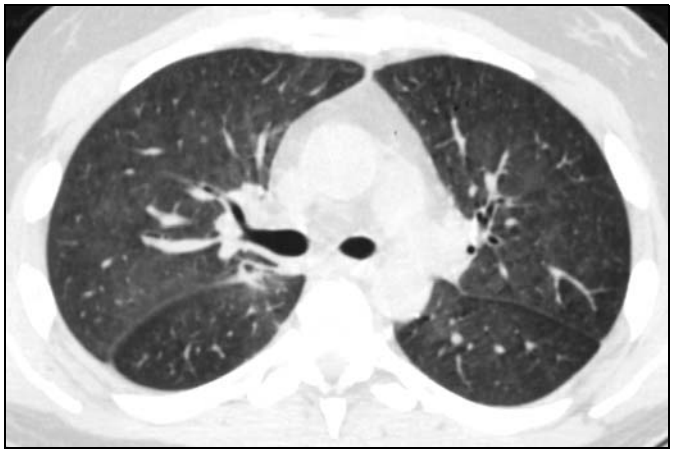

Fig. 2.—36-year-old man with cytomegalovirus pneumonia following renal transplantation. High-resolution CT image through inferior hilum shows isolated diffuse ground-glass opacity widely spread across both lungs.

late winter and early spring and commonly causes fever, cough, dyspnea, and otalgia with clinical signs of rales, rhonchi, or wheezes. In immunocompetent adults, the course usually is self-limited and is treated on an outpatient basis. However, in immunocompromised adults, RSV infection may result in a clinically significant pneumonia [37, 38].

The majority of patients with RSV pulmonary infection will have normal radiographic findings [39]. CT scans in 10 patients with RSV infection following lung transplantation revealed diffuse GGOs in seven patients, pulmonary consolidation in five patients, and tree-in-bud opacities in four patients [40] (Fig. 3).

Other viruses.—Many other viruses commonly produce upper–respiratory tract illnesses and occasionally may produce a limited pneumonia. It is likely that many of these will appear as widespread or small focal regions of GGO, which are self-limited and radiographically resolve spontaneously. Because few of these patients are definitively diagnosed, it is unknown how often ID-GGO is a manifestation of community-acquired viral pneumonias.

Patients Who Have Received Bone Marrow–Suppressing Chemotherapy

In scenario two, a patient receiving bone marrow–suppressing chemotherapy, usually for metastatic carcinoma, presents with respiratory symptoms in the setting of thrombocytopenia and neutropenia. These patients are a special subset of immunocompromised individuals who are at risk for opportunistic infections as a result of neutropenia but who also are at risk for other causes of ID-GGO. These patients frequently are thrombocytopenic and are therefore at increased risk for diffuse aveolar hemorrhage, DAH. They also may develop drug toxicity as a result of the systemic chemotherapies they have received. This leads to the differential of and drug toxicity. In our experience, drug toxicity is the most difficult entity to diagnose and the most common cause of ID-GGO in this population.

In our study of the causes of ID-GGO, drug toxicity accounted for 4% of all pathology-proven cases and therefore represents an important cause of ID-GGO [9]. Because of the wide variety of pharmacologic agents that can result in ID-GGO, there are several histopathologic patterns of drug-related damage to the pulmonary parenchyma. These include noncardiogenic pulmonary edema, diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), DAH, bronchiolitis obliterans with organizing pneumonia (BOOP), hypersensitivity pneumonitis (HP), eosinophilic pneumonia, bronchiolitis obliterans, and venoocclusive disease [41]. Note that the first six patterns of damage listed here often will appear as ID-GGO on CT scans. Drugs, which can cause permeability edema, include cytosine arabinoside (ara-C), gemcitabine, interleukin-2, tumor necrosis factor, and all-transretinoic acid (ATRA). Other chemotherapy medications that have been shown to cause ID-GGO include daunorubicin, bleomycin, vincristine, carmustine, methotrexate, topotecan, carboplatin, and vinorelbine [41] (Figs. 4 and 5). There likely are many more. In a study of drug toxicity in patients with autologous bone marrow transplantation, 65% of cases of drug toxicity manifested as GGO [42].

Outpatients with Slowly Progressive Dyspnea

In this third scenario, an otherwise healthy outpatient will complain of mild chronic dyspnea. Findings of the chest radiograph most often will appear normal or may show a faint haze, which may be interpreted as diffuse GGO. In this situation, ID-GGO most often will indicate one of the following chronic interstitial diseases: HP, desquamative interstitial pneumonia (DIP), respiratory bronchiolitis interstitial lung disease (RBILD), NSIP, acute interstitial pneumonia (AIP), BOOP, and sarcoidosis. Rarely, these patients will have some of the unusual unclassified causes of ID-GGO such as pulmonary alveolar proteinosis (PAP) or bronchoalveolar carcinoma (BAC). A history of smoking may be an important additional factor in this population. DIP and RBILD are seen almost exclusively among smokers and therefore would be unlikely diagnoses in patients who do not smoke.

Chronic Interstitial Diseases Appearing as ID-GGO

An outpatient with chronic respiratory symptoms but without other clinically relevant medical conditions who presents with ID-GGO often will have a chronic interstitial lung disease. In our study of causes of ID-GGO, chronic diffuse interstitial lung diseases accounted for 31% (10/32) of pathology-proven

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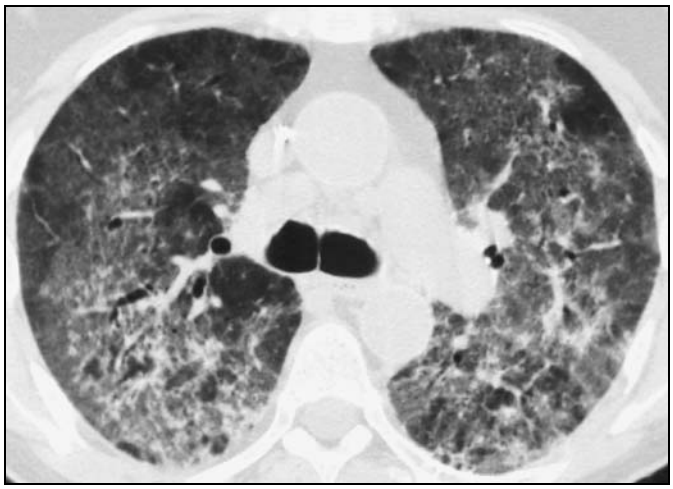

Fig. 3.—65-year-old woman with respiratory syncytial virus pneumonia receiving chemotherapy for ovarian cancer. High-resolution CT image through carina shows extensive ground-glass opacity across both lungs. There also is nonspecific interstitial thickening in more dependent lungs bilaterally; however, ground-glass opacity remains dominant finding.

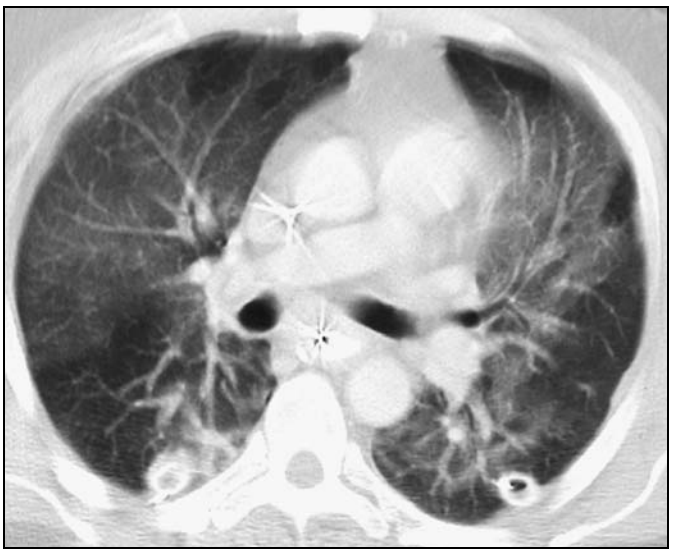

Fig. 4.—75-year-old woman being treated for treated for promyelocytic leukemia and presenting with all-transretinoic acid syndrome of noncardiogenic edema. Thick-section CT image through carina shows widespread ground-glass opacities and small bilateral pleural effusions.

cases [9]. Those interstitial diseases that most likely will present as ID-GGO include HP, DIP, RBILD, and NSIP. Other interstitial diseases that rarely may present as ID-GGO include sarcoidosis and BOOP.

Hypersensitivity pneumonitis.—Inhalation of organic or inorganic particles by sensitized individuals may result in the allergic phenomenon known as HP. In most cases, the allergens are a variety of microorganisms that may reside in decaying vegetable matter such as thermophilic actinomycetes, the *Penicillium* species, the *Aspergillus* species, and the *Mycobacterium avium-intracellulare* complex [43]. A notable exception to this general rule is bird fancier's disease in which the allergens are proteins contained in bird feathers, serum, or guano. Acute HP causes a capillary leak pulmonary edema secondary to an overwhelming allergic response. With lower-dose, chronic exposures, a granulomatous fibrosis develops in the interstitial spaces of the lungs [44].

There are many of causes of HP, including farmer's lung, cotton worker's lung (byssinosis), sugar cane worker's lung (bagassosis), and mushroom worker's diseases [43]. Urban populations can be exposed via contaminated

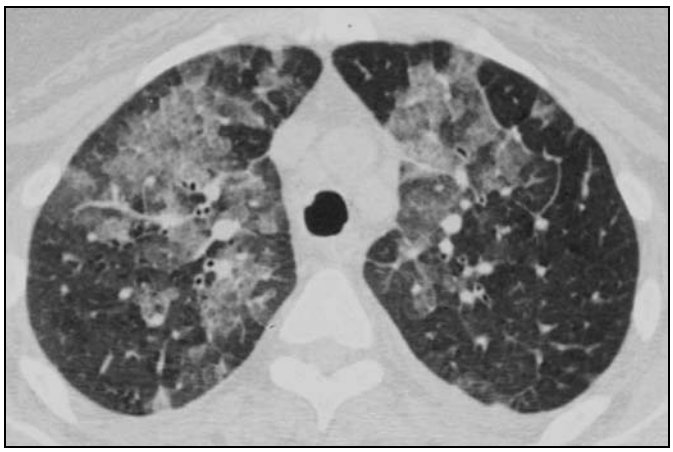

Fig. 5.—37-year-old woman with methotrexate lung toxicity being treated for rheumatoid arthritis. High-resolution CT image through carina shows widespread isolated ground-glass opacities with lobular distribution forming mosaic pattern.

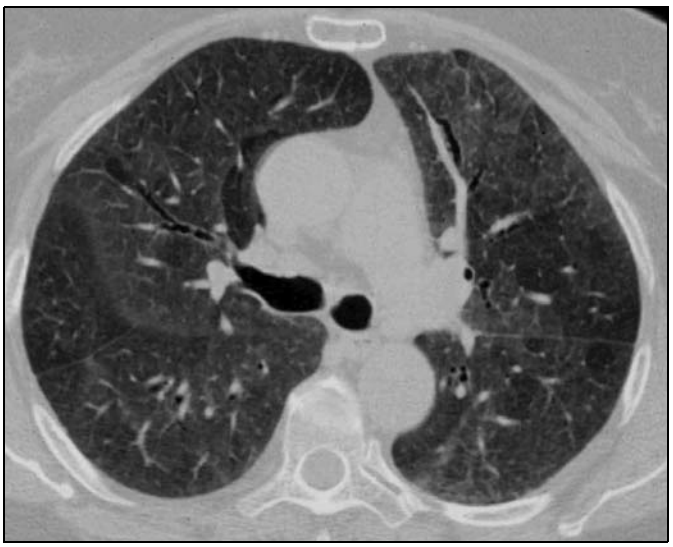

Fig. 6.—29-year-old woman with hypersensitivity pneumonitis, slowly progressive dyspnea, and frequent exposure to birds. High-resolution CT scan of right upper lobe shows poorly defined centrilobular nodules of ground-glass opacity.

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ventilation systems, especially humidifiers and air conditioners. Hobbies such as raising pigeons or parakeets can result in a form of HP called bird fancier's disease.

CT examinations of HP result in a wide spectrum of findings including diffuse alveolar consolidation in acute HP, diffuse nodular interstitial lung disease in subacute and chronic HP, and irregular bands of fibrosis with distortion of the hila in chronic HP [45–49]. However, ID-GGO is among the more common manifestations of subacute HP and, other than pulmonary edema, HP is probably the most common cause of ID-GGOs in normal hosts [45, 47, 49] (Fig. 6). These ID-GGOs often will appear as a mosaic pattern.

Desquamative interstitial pneumonia.—DIP is characterized pathologically by infiltration of alveoli by macrophages associated with mild interstitial fibrosis. In the past, many individuals believed that DIP was an early phase of usual interstitial pneumonia (UIP). Currently, DIP is believed to be a direct result of smoking-related lung toxicity. Patients with DIP typically are between ages of 30 to 50 years and present with chronic progressive dyspnea, with or without fevers [50]. Most patients will improve clinically and radiographically with corticosteroid therapy or smoking cessation [6, 51].

CT scans show ID-GGO in many patients with DIP. Some studies have found that the GGOs predominantly are distributed in the periphery of the lung [52–54]. However, in many other cases, GGOs also may show a diffuse or random distribution (Fig. 7). A pattern of subpleural reticulation may be seen in a minority of patients.

Respiratory bronchiolitis interstitial lung disease.—The histology of RBILD reveals extensive infiltration of alveoli by macrophages associated with mild interstitial fibrosis in a peribronchiolar distribution [55]. Thus, it is histologically identical to DIP with the additional criterion that it be most severe in the centrilobular regions of the secondary pulmonary lobule. This similarity has led some authors to suggest that DIP and RBILD are two manifestations of the same disease [55, 56]. On CT, RBILD often will appear as ID-GGO. Very fine, often centrilobular, nodules also may be apparent on chest CT [56].

Nonspecific interstitial pneumonia.—NSIP represents an interstitial pneumonia that does not meet criteria for UIP, DIP, AIP, or BOOP and thus has a variable histologic and radiologic appearance [57, 58]. It has been associated with collagen vascular disorders, chronic passive congestion, and drug toxicity but is most often an idiopathic disorder. When idiopathic, NSIP most often affects patients in their 40s, 50s, and 60s and presents with an insidious onset of cough and dyspnea [55].

ID-GGOs are the most common radiographic findings in NSIP and are found in nearly 100% of cases. GGO often is found in a subpleural distribution but may also show a random or diffuse distribution [56, 57, 59, 60] (Fig. 8). Reticulation, either randomly or in a subpleural distribution, also is a common finding in one half to four fifths of cases [56, 57, 60, 61]. Irregular linear opacities and traction bronchiectasis also may be seen [56, 59, 60].

Acute interstitial pneumonia.—AIP is a rapidly progressive interstitial fibrosis that resembles the organizing stage of DAD. It usually will present with progressive dyspnea leading to respiratory failure over several weeks or months, and occasionally with an antecedent viral-like prodrome [55]. Chest CT may show alveolar consolidation, GGOs, or both, often with associated traction bronchiectasis [55, 62].

Lymphocytic interstitial pneumonia.—Lymphocytic interstitial pneumonia (LIP) is an idiopathic interstitial abnormality characterized by diffuse lymphocytic infiltration of the interstitium of the lung [63]. It usually is associated with Sjögren's syndrome in adults and HIV infection in children. Some reports have suggested that LIP may represent a precursor to lymphoma or a low-grade lymphoma; however, others suggest that LIP represents a variant of lymphoid hyperplasia and is not a premalignant condition [64–66]. Diffuse GGO appears to be the most common CT finding in LIP and is present in nearly all patients [66–71]. Bronchovascular and septal thickening also have been reported [70, 71]. Thin-walled cysts also may be present in some cases. Serial CT examinations show reversibility of all findings except cysts [70].

Cryptogenic organizing pneumonia and bronchiolitis obliterans with organizing pneumonia.—BOOP is a histologic pattern of lung injury. This often is due to a variety of pulmonary insults such as infectious pneumonia, connective tissue disorders, and bone marrow transplantation. However, in some cases it may have no recognizable cause. The

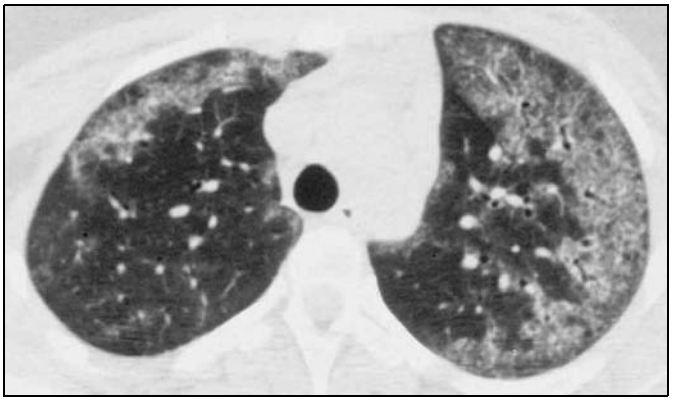

Fig. 7.—72-year-old woman with desquamative interstitial pneumonia, slowly progressive dyspnea, and 40-pack-year history of smoking. High-resolution CT reveals uniform ground-glass opacity.

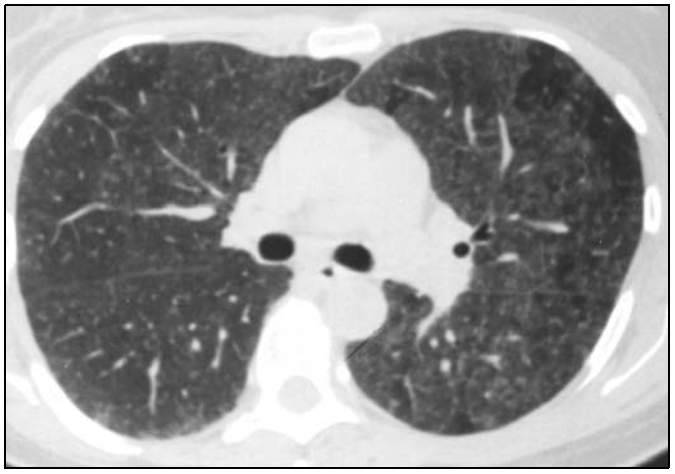

Fig. 8.—26-year-old woman with nonspecific interstitial pneumonia, progressive dyspnea, and positive antinuclear antibodies. High-resolution CT of upper lobes reveals subpleural areas of ground-glass opacity.

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification Conference has identified cryptogenic organizing pneumonia (COP) as the preferred term for idiopathic BOOP [66]. COP is a rare inflammatory condition presenting with progressive dyspnea and often with fever and constitutional symptoms that are unresponsive to standard pneumonia therapies. It is persistent and can lead to serious illness if not treated with corticosteroids, a therapy that in most cases will result in a complete cure of the disease. BOOP, regardless of cause, most often will appear as multifocal alveolar opacities scattered throughout the lungs [72]. Rarely, BOOP may appear as ID-GGO.

Sarcoidosis.—Sarcoidosis is an idiopathic granulomatous disorder with multisystemic ramifications including changes in the meninges, bone, eyes, heart, and skin. Racial predilections include African American and Puerto Rican residents of the United States and West Indians in the United Kingdom. It characteristically presents in patients between the ages of 20 and 40 years but may be encountered at nearly any age.

There are a wide variety of CT manifestations of sarcoidosis. Hilar and mediastinal adenopathy is present in the early and middle stages of the disease. The interstitial lung disease most commonly appears as many small nodules, usually along the bronchovascular bundles but occasionally as randomly distributed interstitial nodules [73–75]. Irregular linear bands of fibrosis, traction bronchiectasis, and coarse cystic spaces may develop in stage IV sarcoidosis. GGOs are among the least common presentations of sarcoidosis (Fig. 9). When GGOs do occur in patients with sarcoidosis, careful inspection of the CT image often will reveal a fine stippled appearance to the GGO, as if it were composed of innumerable, tiny, 1- to 2-mm, ill-defined nodules. Sarcoidosis, HP, and RBILD are the causes of GGO most likely to give this fine stippled appearance. Rarely, sarcoidosis may appear as multiple large ground-glass masses. This pattern is known as alveolar sarcoid. This appearance is virtually pathognomonic of sarcoidosis.

Other Diseases Appearing as ID-GGO

PAP.—Other disorders that present as ID-GGO include PAP and BAC. PAP is a rare, idiopathic disorder of middle-aged adults. Accumulation of protein and lipid-rich material within the lung alveoli results in the subacute onset of slowly progressive and often incapacitating dyspnea [76–78]. This accumulation appears to be a result of an abnormality of surfactant production, metabolism, or clearance. Occasionally PAP may be associated with exposure to a variety of inorganic dusts, most commonly silica, such as is seen in sandblasters [79]. When found in association with silica or other exposures, PAP typically will present with an acute onset of symptoms. Leukemia and lymphoma also may predispose patients to PAP [80, 81]. PAP was fatal in approximately one third of patients before the availability of therapy involving high-volume bronchoalveolar lavage; since the introduction of this therapy, many patients can be cured of the disorder and others may be treated successfully with repeated episodes of bronchoalveolar lavage [82].

Thin-section CT characteristically will show GGOs in association with thickening of the interlobular septa of the secondary pulmonary lobules [83–85] (Fig. 10). This combination of findings has been termed the "crazy paving appearance" and, when present, is quite suggestive of PAP. However, occasionally PAP will present as ID-GGO.

Bronchoalveolar carcinoma.—A form of well-differentiated pulmonary adenocarcinoma, BAC, has a wide variety of radiographic appearances including solitary pulmonary nodules, focal alveolar opacities resembling pneumonia, ground-glass nodules, diffuse alveolar consolidation, and ID-GGOs. Most diffuse BACs will have a dominant mass, nodule, or area of consolidation with associated ID-GGO. Rarely, there will be no such sentinel patch and only ID-GGOs will be present [86].

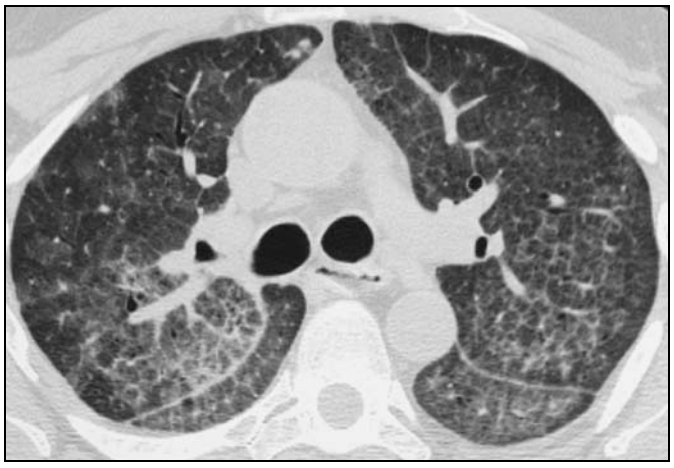

Fig. 9.—46-year-old woman with sarcoidosis who presented with dyspnea and had restrictive pulmonary function tests. High-resolution CT image through carina reveals ground-glass opacities composed of many faint centrilobular nodules widely distributed throughout lungs.

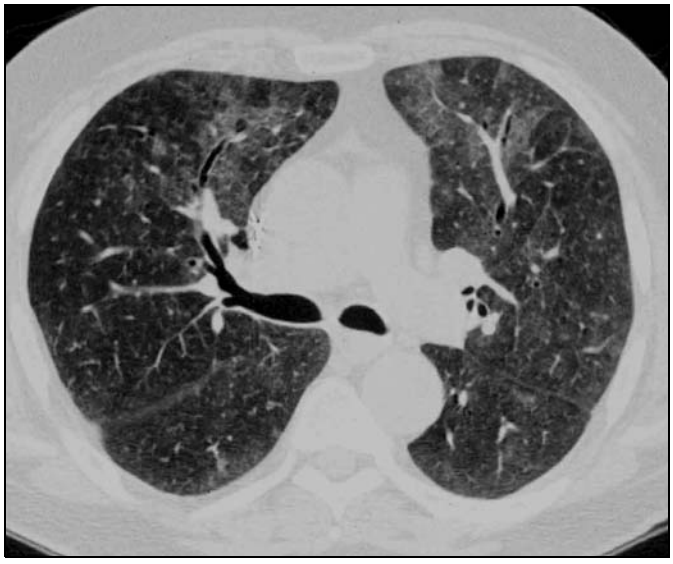

Fig. 10.—53-year-old man with pulmonary alveolar proteinosis. Slowly progressive high-resolution CT image through carina shows presence of ground-glass opacities with slight fine intralobular interstitial thickening. This combination of ground-glass opacities and interstitial thickening has been termed "crazy paving."

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Patients with Acute Development of Dyspnea

In scenario four, the interstitial causes of ID-GGO usually will have a prolonged clinical presentation, and chest radiographs most often will be normal in appearance or show nonspecific interstitial abnormalities. The alveolar causes of ID-GGO usually will present acutely and chest radiographs often will show diffuse alveolar consolidation. ID-GGO in this setting most often will be secondary to one of the acute alveolar causes of ID-GGO: cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS), other causes of permeability edema, or DAH.

Acute Alveolar Diseases Appearing as ID-GGO

In our study of the causes of ID-GGO, acute alveolar diseases such as DAH, cardiogenic edema, and noncardiogenic pulmonary edema accounted for 19% (6/32) of pathology-proven causes of ID-GGO [9]. Because of the need for pathologic proof, pulmonary edema as a cause of ID-GGO is probably underrepresented in this series and pulmonary edema likely represents the single most common cause of ID-GGO. Thus, an acute clinical presentation of respiratory symptoms in a patient with ID-GGO should raise the possibility of hydrostatic and capillary leak pulmonary edema and DAH.

Pulmonary Edema

Pulmonary edema is a result of imbalances in the Starling forces, which govern the transport of fluids between the vascular and interstitial spaces of the lung. During homeostasis, there is a near balance between these forces, and the small net transfer of fluid into the interstitium is removed via the pulmonary lymphatics. However, a disturbance of this equilibrium will lead to excessive transport of water and solutes into the interstitial space. If the process continues, the interstitial lymphatics become overwhelmed and fluid overflows into the alveoli, leading to alveolar edema [87].

Typically, pulmonary edema is subdivided into two major etiologic subcategories: hydrostatic pulmonary edema and increased permeability pulmonary edema. In hydrostatic edema, there is increased intravascular hydrostatic pressure, which results in a net force driving water and solutes into the interstitial and, subsequently, alveolar spaces of the lung. Hydrostatic edema most often is a manifestation of left-sided heart failure. Increased permeability edema usually is a result of disruption of the capillary epithelial membrane, which allows plasma proteins to pass into the interstitial space. These proteins exert an osmotic force drawing water into the interstitial space, and if of sufficient volume, they spill into the alveolar spaces [87]. Permeability edema most often is a result of ARDS but has a number of other causes.

Cardiogenic pulmonary edema.—Left-sided heart failure is by far the most common cause of hydrostatic edema and thus commonly is known as cardiogenic pulmonary edema. On thin-section CT, the most common manifestation of cardiogenic pulmonary edema is ID-GGO (Fig. 11). CT also may show thickening of the interlobular septa. The GGOs associated with hydrostatic edema often will have a central, perihilar distribution and be associated with enlarged pulmonary vessels and an enlarged heart.

Adult respiratory distress syndrome.—ARDS is the most common cause of noncardiogenic pulmonary edema and is a common physiologic response to a wide variety of insults including sepsis, aspiration of gastric contents, overwhelming pneumonia, severe trauma, multiple fractures, major burns, pancreatitis, prolonged hypotension, disseminated intravascular coagulation, drug overdose, and thoracic surgery [88, 89].

CT scans of ARDS most often will show bilateral GGO, pulmonary consolidation, or a combination of both [90, 91]. ID-GGO is most often a manifestation of the earlier exudative phase of disease [90, 91]. Pulmonary opacities often will be most severe in the

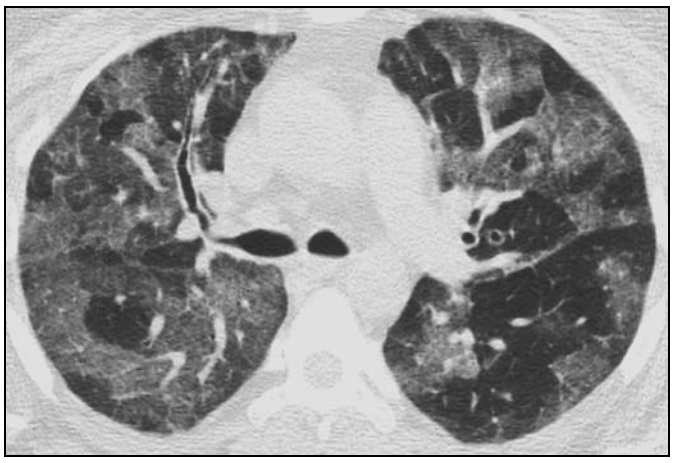

Fig. 11.—44-year-old man with cardiogenic edema and with acute onset of dyspnea and history of mitral stenosis. High-resolution CT image through great vessels shows geographic ground-glass opacity.

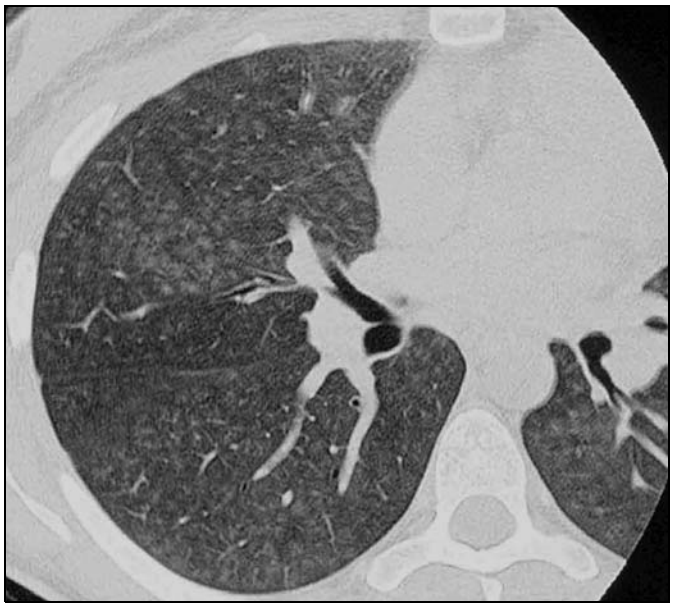

Fig. 12.—60-year-old man with diffuse alveolar hemorrhage and with acute onset of dyspnea and history of Wegener's granulomatosis. High-resolution CT image through right upper lobe bronchus reveals randomly distributed ground-glass opacities.

TABLE 2 Clinical Scenarios and Differential Diagnoses of Patients with Isolated Diffuse Ground-Glass Opacity

Scenario	Disease Category	Differential Diagnoses
Immunosuppressed (HIV, transplant)	Opportunistic infections	PCP, CMV, HSV, RSV, other viruses
Bone marrow suppression	Opportunistic infections	PCP, CMV, HSV, RSV, other viruses
	Acute alveolar disease	DAH
	Miscellaneous	Drug toxicity
Slowly progressive dyspnea	Chronic interstitial disease	HP, DIP, AIP, NSIP, RBILD, sarcoidosis
	Miscellaneous	BOOP, PAP, BAC
IP/OP acute dyspnea	Acute alveolar disease	CHF, ARDS, noncardiogenic edema, DAH
Debilitated hospital patient	Acute alveolar disease	CHF, ARDS, volume overload

Note.—PCP = pneumocystis pneumonia, CMV = cytomegalovirus pneumonia, HSV = herpes simplex virus pneumonia, RSV = respiratory syncytical virus, DIP = desquamative interstitial pneumonia, RBILD = respiratory bronchiolitis interstitial pneumonia, HP = hypersensitivity pneumonitis, NSIP = nonspecific interstitial pneumonia, AIP = acute interstitial pneumonia, BOOP = bronchiolitis obliterans with organizing pneumonia, PAP = pulmonary alveolar proteinosis, BAC = bronchoalveolar carcinoma, DAH = diffuse alveolar hemorrhage, CHF = cardiogenic pulmonary edema, ARDS = adult respiratory distress syndrome, IP/OP = inpatient/outpatient.

more gravity-dependent regions of the lung. Unlike chest radiographs, which characteristically show uniform consolidation across the lung parenchyma, 75% of the time CT scan opacification will appear inhomogeneous or patchy.

Other noncardiogenic pulmonary edema.—It is likely that all causes of pulmonary edema can occasionally result in ID-GGO (Fig. 4). ID-GGO has been reported in cases of near drowning [92] and fat emboli syndrome [93].

Diffuse Alveolar Hemorrhage

Alveolar hemorrhage may result from a large number of disorders; however, when the process is diffuse, the differential diagnosis is moderately limited. The most common causes of DAH in outpatients are the group of entities often referred to as the pulmonary–renal syndromes [19]. Goodpasture's syndrome, Wegener's granulomatosis, and systemic lupus erythematosus are prime examples. Although these disorders may have other pulmonary manifestations, DAH is among the most common radiographically identifiable abnormality. Vasculitises other than Wegener's granulomatosis, such as Churg-Strauss vasculitis and microscopic polyangiitis, also are less common causes of DAH. Patients with lymphoma and leukemia also are inclined to DAH as a result of platelet deficiency or platelet malfunction. DAH is a feared complication of bone marrow transplantation because of its high mortality in this population [94]. Bleeding disorders such as antiphospholipid-antibody syndrome and use of anticoagulatory drugs also may predispose patients to DAH.

CT scans of DAHs may reveal frank consolidation with obliteration of the pulmonary vascular markings, but often they will appear as ID-GGOs (Fig. 12). On thin-section CT images, ID-GGO may be spread uniformly throughout the lung, be randomly distributed, appear as centrilobular opacities, or have a mosaic pattern.

Acutely Ill Hospitalized Patients

In scenario five, it is quite common for generally debilitated hospitalized patients to undergo CT scanning for a wide variety of clinical indications unrelated to dyspnea or hypoxia. For example, chest CT scans often will be obtained on ICU patients to search for causes of a persistent fever. These patients represent a subset of scenario four: patients with the acute development of dyspnea. ID-GGO in these patients most often will signify mild interstitial pulmonary edema due to congestive heart failure, volume overload, or ARDS. It is rare for these patients to have predisposing conditions for DAH or the more unusual causes of pulmonary edema, and therefore, the differential diagnosis is further limited in this patient population in comparison with those of the more general scenario four.

Conclusion

Unlike GGOs, in the company of other imaging findings ID-GGOs are caused by a relatively limited group of diseases. These can be grouped into four large categories of disease: diffuse pneumonias, some chronic interstitial diseases, acute alveolar diseases, and a group of unusual miscellaneous disorders. Furthermore, the presentation of ID-GGO often falls into one of five clinical scenarios: patients who are immunocompromised, patients who are receiving bone marrow–suppressing medications, outpatients who have slowly progressive dyspnea, inpatients and outpatients who have acutely developing dyspnea, and inpatients who are acutely ill. These clinical scenarios engender limited differential diagnoses in most cases, as outlined in Table 2.

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