Imaging Features of Pulmonary Kaposi Sarcoma–Associated Immune Reconstitution Syndrome

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OBJECTIVE. The purpose of this study was to analyze the radiologic features of pulmonary Kaposi sarcoma–associated immune reconstitution syndrome. The syndrome is a phenomenon characterized by clinical deterioration of the condition of HIV-positive patients after initiation of highly active antiretroviral therapy.

MATERIALS AND METHODS. The study included four patients at our institution who fulfilled the diagnostic criteria for pulmonary Kaposi sarcoma–associated immune reconstitution syndrome from 2001 to 2006. All patients were men (mean age, 43 years; range, 31–59 years). Images reviewed included chest radiographs obtained before highly active antiretroviral therapy, radiographs and chest CT scans obtained at appearance of the symptoms of Kaposi sarcoma–associated immune reconstitution syndrome, and follow-up radiographs and chest CT scans during immune reconstitution syndrome.

RESULTS. The radiographic findings of Kaposi sarcoma–associated immune reconstitution syndrome included reticular and reticulonodular opacities ($n = 4$), areas of consolidation ($n = 3$), septal lines ($n = 3$), and pleural effusion ($n = 3$). The CT findings in all four patients were ill-defined pulmonary nodules and interlobular septal thickening. Three of the patients had a CT halo sign, areas of consolidation, ground-glass opacities, lymphadenopathy, and pleural effusion. The areas of consolidation in three subjects who did not receive chemotherapy increased markedly after 14–20 days. CT performed during the initial symptoms of immune reconstitution syndrome in these three subjects showed less than 5% parenchymal involvement. Follow-up CT showed 26–50% involvement in two patients and more than 50% involvement in one patient.

CONCLUSION. The radiologic findings of pulmonary Kaposi sarcoma–associated immune reconstitution syndrome are similar to the findings described in patients with Kaposi sarcoma without the syndrome, but the extent of abnormalities tends to increase with the development of the syndrome.

Since the introduction of highly active antiretroviral therapy (HAART), there has been a significant decrease in AIDS-related morbidity and mortality as a result of suppression of HIV replication and immune reconstitution in most treated patients with HIV infection [1, 2]. Despite the undeniable benefits of HAART in preventing opportunistic infections and malignant disease, these conditions may temporarily worsen when antiretroviral therapy is started, a clinical response known as immune reconstitution syndrome [3–8]. This syndrome is an inflammatory reaction against microbiologic pathogens and antigens that occurs soon after initiation of HAART and is characterized by a deterioration in clinical condition despite improvement in the HIV RNA level and, usually, by an increase in CD4 cell count [3–8]. Immune reconstitution syndrome can occur during or soon after a patient is treated for an opportunistic infection or as a new clinical manifestation of a previously subclinical infection [3, 9, 10]. The pathogenesis of immune reconstitution syndrome is still unclear but probably involves HAART-induced restoration of pathogen-specific immune responses against infectious and noninfectious antigens [3, 4, 7–11]. Other names for this syndrome are immune restoration syndrome, immune reconstitution inflammatory syndrome, and immune reconstitution phenomenon [3–5].

Immune reconstitution syndrome has been characterized in a variety of HIV-related opportunistic diseases, including *Mycobacterium avium* complex infection, *Mycobacterium tuberculosis* infection, cryptococcosis,

TABLE 1: Clinical and Laboratory Findings of Pulmonary Kaposi Sarcoma–Associated Immune Reconstitution Syndrome (*n* = 9)

Age (y)/Sex	Time Between HAART Initiation and Flare of Kaposi Sarcoma (wk)	CD4 Cell Count (/μL) Before HAART	CD4 Cell Count (/μL) at Diagnosis of Syndrome	HIV RNA Level (copies/mL) Before HAART	HIV RNA Level (copies/mL) at Diagnosis of Syndrome	Presentation of Kaposi Sarcoma	Outcome
Current series							
59/M	12	90	160	> 100,000	< 50	Pulmonary and mucocutaneous	Died
31/M	22	40	120	81,500	< 50	Pulmonary and mucocutaneous	Died
36/M	2	10	10	18,800	< 50	Pulmonary and cutaneous	Improved after chemotherapy
44/M	1	< 10	NA	25,600	NA	Pulmonary and mucocutaneous	Died
Shelburne et al. [4]							
NR	3	48	169	> 750,000	1,377	Pulmonary and cutaneous	NR
Harindra and Foley [17]							
40/M	4	< 10	120	166,466	2,064	Pulmonary and cutaneous	Died
Crane et al. [16]							
47/M	6	150	135	> 500,000	1,990	Pulmonary and cutaneous	Died
Sánchez Ayuso et al. [18]							
37/M	4	NR	100	NR	718	Pulmonary and lymphatic	Died
Ball [19]							
43/M	2	23	24	1,800,000	2,282	Pulmonary and mucocutaneous	Improved after chemotherapy

Note—HAART = highly active antiretroviral therapy, NA = not available, NR = not reported.

cytomegalovirus infection, *Pneumocystis jiroveci* pneumonia, herpes zoster, and progressive multifocal leukoencephalopathy [4–6, 10, 11]. It is estimated that 10–25% of patients who start HAART experience immune reconstitution syndrome [10].

HAART is a key component in the management of Kaposi sarcoma (KS) in patients with HIV infection and often leads to stabilization and regression of KS lesions [12–15]. Occasional reports [4, 6–8, 16–22], however, describe marked clinical deterioration after initiation of HAART, the signs and symptoms being consistent with KS-associated immune reconstitution syndrome. The aim of our study was to analyze the radiographic and CT findings of pulmonary KS-associated immune reconstitution syndrome.

Materials and Methods

The study included four patients consecutively registered at our institution from 2001 to 2006 and fulfilling the diagnostic criteria for pulmonary KS-associated immune reconstitution syndrome (Table 1). All patients were men 31–59 years old (mean age, 43 years). The diagnosis was established by the presence of the following criteria: biopsy-proven KS in skin,

mucosa, or lymph node associated with pulmonary radiologic findings in keeping with KS (*n* = 3) or pulmonary KS found at autopsy (*n* = 1) without evidence of other pulmonary disease or infection (*n* = 4); temporal association between initiation of HAART and worsening of pulmonary signs and symptoms associated with concomitant worsening of cutaneous and/or mucosal KS lesions (*n* = 4); favorable response to HAART (> 1 $\log_{10}$ reduction in HIV RNA) with or without an associated 50% CD4 increase to ≥ 50 cells/μL (*n* = 3); and exclusion of infectious entities with extensive clinical and laboratory investigation (*n* = 4). The case definition was based on previously reported diagnostic criteria [4, 5, 10, 11]. All patients underwent bronchoscopy: the findings were within normal limits in all patients, and microbiology and special stains were negative.

The HAART regimens consisted of two nucleosides combined with a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor. HIV RNA and CD4+ cell count were measured before initiation of antiretroviral therapy in all four cases and at the time of diagnosis of KS-associated immune reconstitution syndrome in three cases. The immune response to HAART was reflected by a reduction in HIV RNA $\log_{10}$ of 2.6, 3.0, and 3.3 in the three cases in which comparison was available. One patient had

no increase in CD4 cell count, and two patients had increases from 90 and 40 cells/μL to 160 and 120 cells/μL, respectively. In the fourth case, HIV RNA and CD4 cell count after initiation of HAART were not measured because the patient died after rapid deterioration of his clinical condition. The mean interval from the start of HAART and establishment of the diagnosis of KS-associated immune reconstitution syndrome was 9.2 weeks (range, 1–22 weeks).

The images of the four patients were reviewed retrospectively. Two experienced radiologists jointly interpreted the chest radiographs and thoracic CT scans and reached a decision by consensus. The reviewers were aware that all patients had the diagnosis of KS-associated immune reconstitution syndrome. Images reviewed in the study included one chest radiograph per patient obtained before initiation of HAART, except in one case, in which the only radiographs obtained before HAART were acquired during an episode of *P. jiroveci* (*Pneumocystis carinii*) pneumonia and therefore were excluded; one radiograph and chest CT scan per patient obtained during initial symptoms of KS-associated immune reconstitution syndrome; and one follow-up radiograph and chest CT scan per patient obtained during immune reconstitution syndrome.

TABLE 2: Radiographic Findings Before Initiation of Highly Active Antiretroviral Therapy (HAART) and During Pulmonary Kaposi Sarcoma–Associated Immune Reconstitution Syndrome (IRS)

Case	Time	Consolidation	Reticular Opacities	Reticulonodular Opacities	Pleural Effusion	Kerley B Lines
1	Before HAART	Absent	Mild	Absent	Absent	Absent
	At IRS presentation	Moderate	Moderate	Absent	Mild	Mild
	At follow-up	Severe	Severe	Absent	Moderate	Severe
2	Before HAART	NA	NA	NA	NA	NA
	At IRS presentation	Mild	Absent	Moderate	Mild	Moderate
	At follow-up	Moderate	Absent	Severe	Moderate	Moderate
3	Before HAART	Absent	Absent	Mild	Absent	Mild
	At IRS presentation	Absent	Absent	Moderate	Absent	Mild
	At follow-up after chemotherapy	Absent	Absent	Moderate	Absent	Mild
4	Before HAART	Absent	Absent	Mild	Absent	Absent
	At IRS presentation	Absent	Absent	Mild	Absent	Absent
	At follow-up	Moderate	Absent	Severe	Mild	Absent

Note—NA = not available.

The CT scans were obtained with a 4-MDCT scanner (LightSpeed Plus, GE Healthcare). The scans were acquired at end inspiration from the apex of the lung to the diaphragm at 120 kV and 210 mA and reconstructed to slice thicknesses of 1.0 mm (*n* = 2), 1.25 mm (*n* = 2), and 5 mm (*n* = 4). In one case, follow-up CT was performed 105 days after the initial CT scan, after the patient underwent chemotherapy. The other patients did not undergo chemotherapy and underwent follow-up CT 14–20 days after the initial CT examination (mean, 16 days). A total of eight chest radiographs obtained during KS-associated immune reconstitution syndrome were reviewed, two per patient. These radiographs were acquired 1–72 days after the CT scans (mean interval, 10.5 ± 24.9 days).

Chest radiographs were reviewed for hilar and mediastinal lymphadenopathy, reticular and reticulonodular opacities, Kerley B lines, parenchymal consolidation, pulmonary nodules, and pleural effusions. The chest CT scans were reviewed for the presence or absence and anatomic distribution of ground-glass opacities, consolidation, nodules, interlobular septal thickening, peribronchovascular thickening, irregular linear opacities (reticulation), the halo sign, emphysema, pulmonary cysts, mediastinal, hilar, and axillary lymphadenopathy, pleural nodularity, and pleural effusion. These findings were defined according to the Fleischner Society nomenclature [23].

The radiologic findings were classified by one chest radiologist as mild, moderate, or severe on the basis of visual assessment of extent and severity to characterize progression, stability, or regression of disease. The extent of consolidation was classified as involving less than 5%, 5–25%, 26–50%, or more than 50% of the pulmonary parenchyma. These scores were based on visual assessment of the per-centage of involvement of each lobe (the lingula was considered a separate lobe) as approximately 0, 1/4, 2/4, 3/4, or 4/4. Each lower lobe was considered to represent 20% of the pulmonary parenchyma; the upper lobes, right middle lobe, and lingula were considered to represent 15% each. The overall pulmonary extent of consolidation represented the sum of the lobar extent. Pulmonary nodules were classified as having well-defined or ill-defined margins. Axillary, mediastinal, or hilar lymphadenopathy was considered present when the lymph node short-axis diameter was greater than 10 mm. When present, lymphadenopathy was classified as mild when the nodal diameter was less than 20 mm, moderate when the diameter was between 20 and 30 mm, and severe when the diameter was greater than 30 mm.

The anatomic distribution of the abnormalities on chest radiographs was classified as predominantly in the upper, middle, or lower lung zone and perihilar, peripheral, or random. On CT the anatomic distribution was classified as follows: central when there was a predominance of abnormalities in the inner third of the lung, peripheral when there was a predominance of abnormalities in the outer third of the lung, and random when there was no central or peripheral predominance. Zonal predominance was assessed as being upper, middle, lower, or random. Upper lung zone predominance was considered present when most of the abnormalities were above the level of the tracheal carina, middle zone predominance when between the carina and the inferior pulmonary veins, lower zone predominance when most of the abnormalities were below this level, and random when there was no zonal predominance. The findings also were classified as unilateral or bilateral. The images were reviewed with lung (width, 1,500 H; level, –600 H) and mediastinal (width, 350 H; level, 35–40 H) windows.

Results

All patients had abnormal chest radiographic and CT findings at presentation and follow-up of KS-associated immune reconstitution syndrome (Tables 2 and 3). Chest radiographs showed reticular opacities in one of the four patients, ill-defined nodules associated with reticular opacities in three, and septal (Kerley B) lines in three patients (Figs. 1 and 2). Consolidation was found on the radiographs of two patients during the onset of KS-associated immune reconstitution syndrome and in three patients on the follow-up radiograph (Figs. 1 and 2). The radiographic findings were predominantly located in a perihilar distribution in three of the four patients and were diffuse in the other patient. The abnormalities involved mainly the middle and lower lung zones in three patients and showed no predominance in the other patient. Pleural effusion was present in two patients on the radiograph during the onset of immune reconstitution syndrome and in three patients on the follow-up radiograph. Mediastinal and hilar lymphadenopathy were not detected in any of the four subjects.

The chest radiograph obtained before initiation of HAART was compared with a radiograph obtained during the onset of KS-associated immune reconstitution syndrome in three of the four cases. The latter radiographs showed mild progression of the abnormalities in one patient and marked progression in the other two patients (Table 2). Comparison between the chest radiograph obtained during the onset of KS-associated immune reconstitution syndrome and the follow-up radiograph was performed in all four patients. Rapid progres-

TABLE 3: CT Findings of Pulmonary Kaposi Sarcoma–Associated Immune Reconstitution Syndrome (IRS)

Case	Time	Consolidation	Nodules	Halo Sign	Ground-Glass Opacities	Peribronchovascular and Interlobular Septal Thickening	Lymphadenopathy	Pleural Effusion
1	At IRS presentation	Mild	Mild	Absent	Mild	Mild	Mild	Mild
	At follow-up	Moderate	Mild	Absent	Moderate	Moderate	Mild	Moderate
2	At IRS presentation	Mild	Mild	Mild	Mild	Mild	Mild	Mild
	At follow-up	Severe	Moderate	Mild	Severe	Moderate	Mild	Severe
3	At IRS presentation	Absent	Mild	Mild	Absent	Mild	Absent	Absent
	At follow-up after chemotherapy	Absent	Mild	Mild	Absent	Mild	Absent	Absent
4	At IRS presentation	Mild	Mild	Mild	Mild	Mild	Mild	Absent
	At follow-up	Moderate	Moderate	Mild	Moderate	Moderate	Mild	Moderate

sion of the abnormalities was found in the three patients who did not receive chemotherapy. Subtle improvement was found in the patient who received chemotherapy.

Irregular and ill-defined pulmonary nodules measuring 3–27 mm in diameter (Figs. 2 and 3) were found on CT scans of all patients. The halo sign, consolidation, and ground-glass opacities were present in three patients (Figs. 2–4). When present, nodules, consolidations, and ground-glass opacities were bilateral in all patients. These findings had lower-zone predominance in two patients, middle zone predominance in one patient, and no zonal predominance in one patient. The anatomic distribution was predominantly central peribronchovascular in all patients. The consolidations in the three patients who did not undergo chemotherapy increased in extent during the 14- to 20-day follow-up period. The consolidations involved less than 5% of the parenchyma on the initial CT scans of all three patients, 26–50% in two patients, and more than 50% in one patient at follow-up evaluation.

Peribronchovascular and interlobular septal thickening was found in all subjects (Figs. 2–4). Pulmonary cysts and paraseptal and centrilobular emphysema were found in one patient each. Pleural nodularity was present in three patients (Fig. 2). Pleural effusion was present in two of the subjects on initial CT and in three on follow-up CT (Figs. 2–4). Mediastinal and axillary lymphadenopathy were found in three and two of the patients, respectively. When present, lymphadenopathy had high attenuation (38–95 H; mean, 68.8 ± 20.6 H) on CT scans obtained after contrast administration.

Discussion

KS is the most common tumor among patients with HIV infection, occurring predomi-

nantly among homosexual or bisexual men [24]. KS is associated with human herpesvirus 8 infection [24, 25]. Previous studies [1, 13, 24, 26–28] have shown that use of HAART has resulted in substantial diminution in the incidence, morbidity, and mortality of KS. Furthermore, HAART alone can lead to stabilization and regression of KS, often eliminating the need for chemotherapy and radiation therapy in the treatment of many patients with HIV infection [14] and prolonging remission among patients with a complete response [15]. Holkova et al. [13] analyzed the cases of 37 consecutively registered patients with pulmonary KS and HIV infection and found that 90% of the patients in the pre-HAART period died of progressive pulmonary KS, a finding in agreement with other published data. In the post-HAART period, 47% of patients died of progressive pulmonary KS, a significant improvement in overall survival rate.

Although in most cases of KS clinical improvement occurs after HAART, KS-associated immune reconstitution syndrome after initiation of HAART has been reported [3, 4, 6–8, 16–22]. The onset of the syndrome is probably related to an increased immune response to human herpesvirus 8 characterized by inflammation, edema, and worsening of KS lesions. To our knowledge, in 1997 Weir and Wansbrough-Jones [20] described the first case of KS flare. The patient experienced airway obstruction as a result of worsening KS of the larynx 4 weeks after the start of HAART despite improvement in the CD4 cell count and effective HIV viral suppression. Connick et al. [7] later reported one case of KS-associated immune reconstitution syndrome in a patient with cutaneous lesions consistent with KS. During the second week of HAART, face and neck swelling, new cutaneous lesions, and cervical lymphadenopathy developed, and exci-

sional biopsy proved the diagnosis of KS. The patient's condition improved after chemotherapy. Rodríguez-Rosado et al. [22] also reported a case of cutaneous KS that exhibited an explosive increase in number and size of the lesions and the development of lymphedema after the initiation of HAART. Shelburne et al. [4] described one case in which recovery of the immune system with HAART resulted in worsening of both sarcoidosis and cutaneous KS. Bower et al. [8] reported a 6.6% incidence of KS-associated immune reconstitution syndrome among 150 patients with KS who started HAART. In these cases, none of the patients with immune reconstitution syndrome had pulmonary KS. Similarly, Leidner and Aboulafia [6] reported nine cases of cutaneous, mucocutaneous, or lymphatic KS-associated immune reconstitution syndrome.

Although most previous reports describe cases of KS-associated immune reconstitution syndrome with no visceral involvement, there are reports [4, 16, 18, 19] of pulmonary KS-associated immune reconstitution syndrome (Table 1). The data on the radiologic findings in these patients, however, are limited. Crane et al. [16] described a patient with a fatal inflammatory response to pulmonary KS after initiation of HAART. The chest radiograph was described as having a prominent interstitium and small pleural effusion. The chest CT findings confirmed the radiographic findings and showed splenomegaly and lymphadenopathy. Sánchez Ayuso et al. [18] described a case of fatal pulmonary KS-associated immune reconstitution syndrome. In that case, CT of the thorax showed mediastinal and bilateral axillary lymphadenopathy, paraseptal emphysema, consolidation, ill-defined nodular opacities, ground-glass opacities, and interlobular septal thickening with a predominant central distribution. Ball [19] reported a case of pulmonary KS that worsened after initiation of
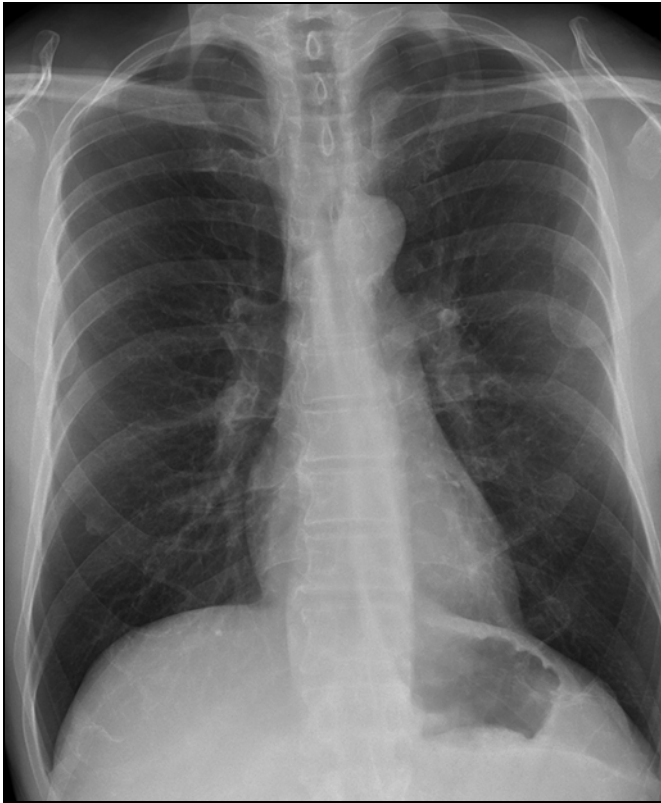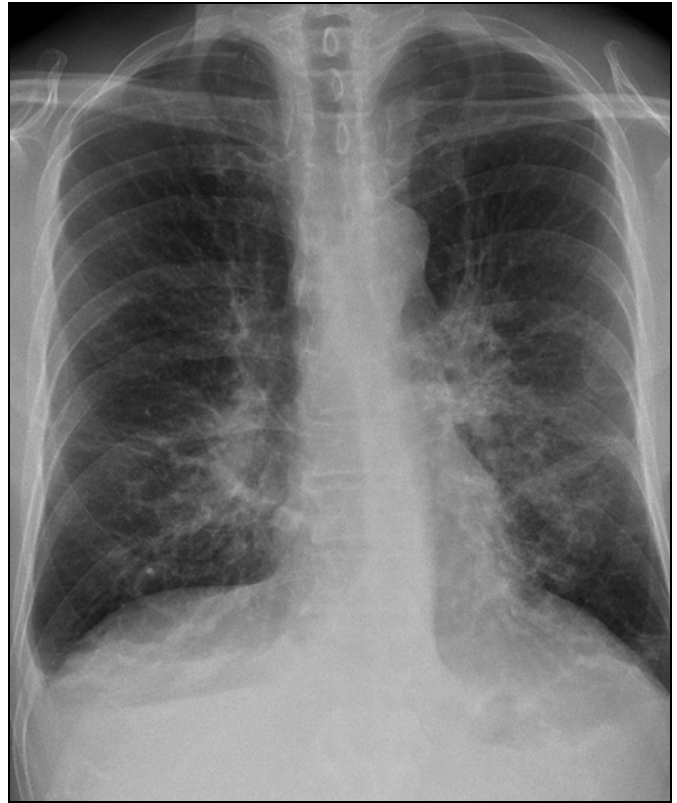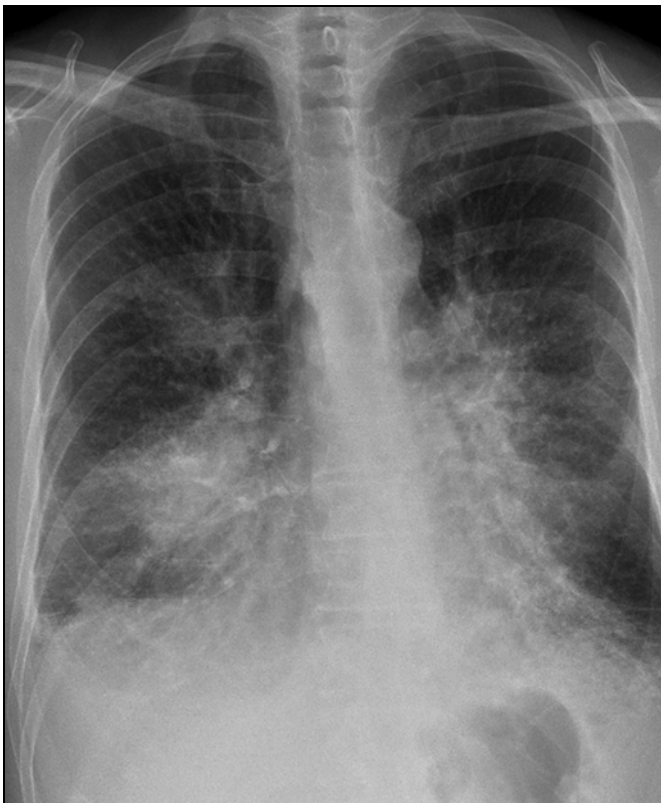
Fig. 1—59-year-old man with autopsy-confirmed Kaposi sarcoma–associated immune reconstitution syndrome.

A, Chest radiograph before onset of immune reconstitution syndrome shows mild reticular opacities in predominantly perihilar distribution.

B, Chest radiograph obtained during initial symptoms of Kaposi sarcoma–associated immune reconstitution syndrome shows increase in reticular opacities and development of areas of consolidation associated with Kerley B lines and small pleural effusions.

C, Follow-up chest radiograph obtained 17 days after **B** shows rapid increase in amount of consolidation, reticular opacities, and pleural effusion.
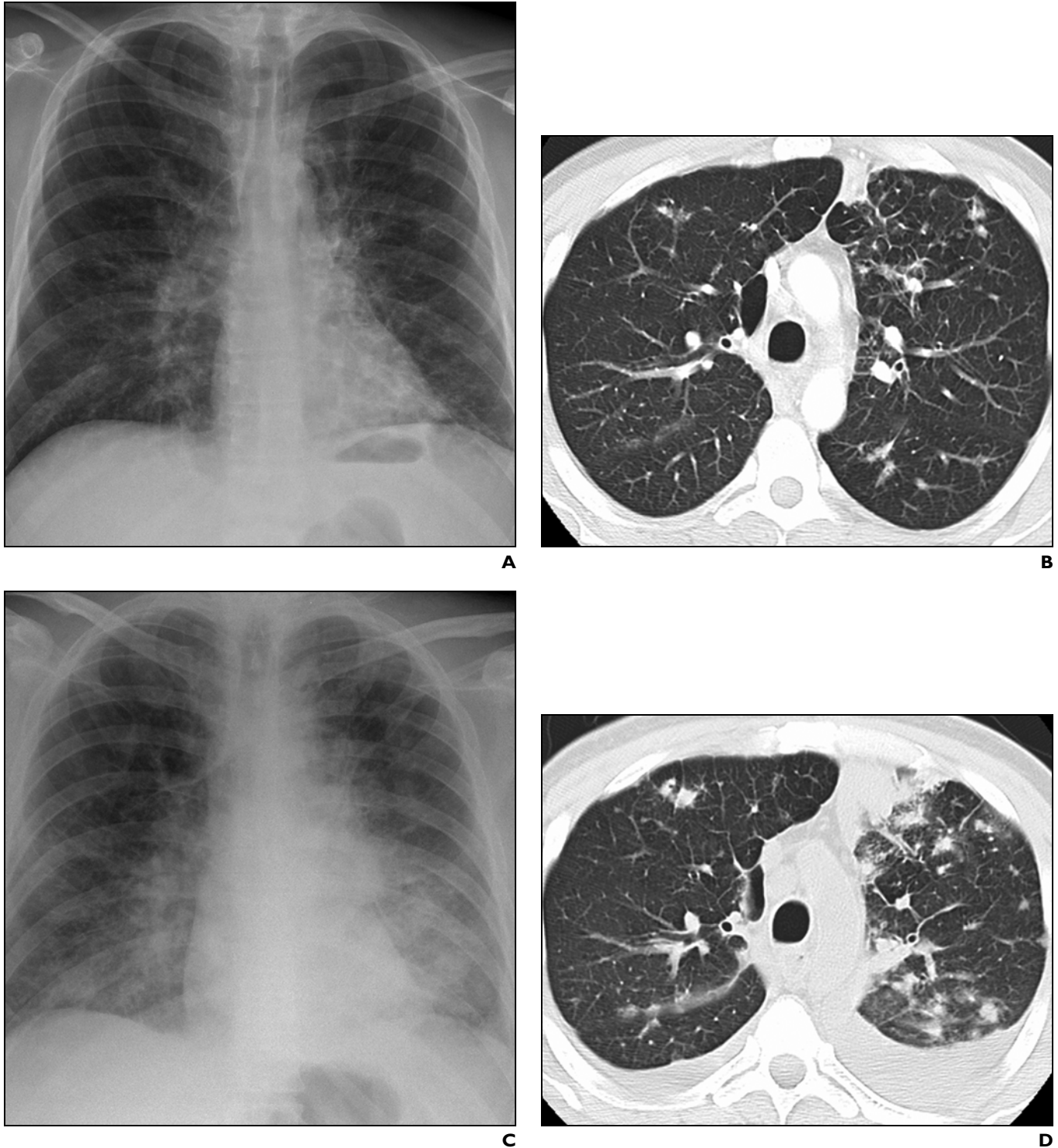
Fig. 2—44-year-old man with Kaposi sarcoma–associated immune reconstitution syndrome.
A, Chest radiograph obtained during onset of immune reconstitution syndrome shows reticulonodular opacities in predominantly perihilar distribution.
B, CT scan (5-mm slice thickness reconstruction) shows bilateral irregular nodules, lobular consolidation in left upper lobe, interlobular septal thickening, and fissural nodularity.
C, Follow-up chest radiograph obtained 16 days after **A** shows increase in nodular opacities and development of areas of consolidation and bilateral pleural effusions.
D, Follow-up CT scan (5-mm slice thickness reconstruction) obtained 14 days after **B** shows increase in size and number of nodules, some with halo sign, increase in extent of consolidation and interlobular septal thickening, and development of bilateral pleural effusions.
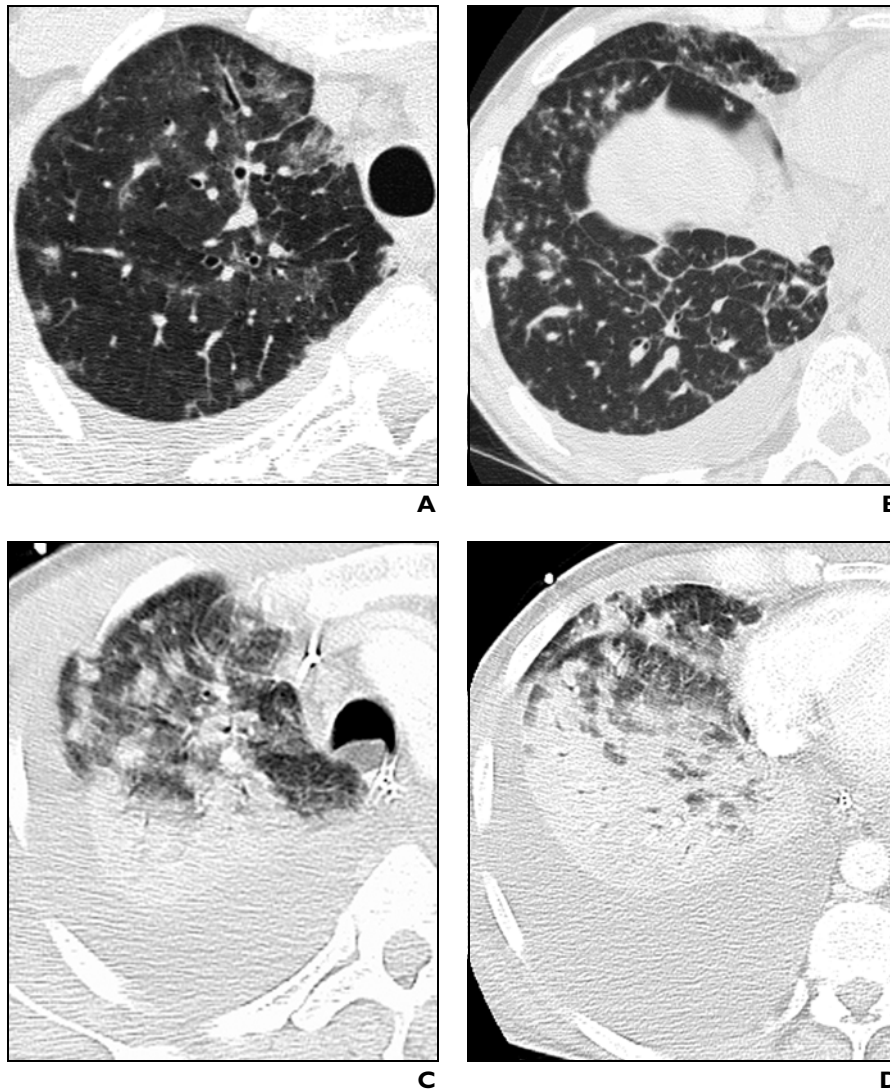
Fig. 3—31-year-old man with Kaposi sarcoma–associated immune reconstitution syndrome.
A, CT scan (1.25-mm slice thickness reconstruction) of right upper lobe shows ground-glass opacities, irregular ill-defined nodules with ground-glass halo (halo sign), and pleural effusion.
B, CT scan (1.25-mm slice thickness reconstruction) of right lower lobe shows irregular nodules, interlobular septal thickening, and pleural effusion.
C and **D,** CT scans (5-mm slice thickness reconstruction) of right upper lobe (**C**) and right lower lobe (**D**) obtained 21 days after **A** and **B** show extensive progression of disease characterized by increase in number and size of nodules, confluence of nodules, development of consolidation, and increase in pleural fluid.

18, 19] mentioning radiologic findings, no study has been focused on the imaging features of pulmonary KS-associated immune reconstitution syndrome. The well-known characteristic radiographic finding of AIDS-related KS is the presence of bilateral interstitial or alveolar opacities, often associated with poorly defined nodular opacities [30–33]. These findings are frequently accompanied by pleural effusions, occurring in as many as 67% of patients [30–34]. Lymphadenopathy is present in nearly 10% of cases [30, 31, 34]. Peripheral linear opacities (Kerley B lines) also have been reported [31]. In a few patients with minimal involvement of the lung, the chest radiographic findings may be normal [30, 31, 34].

The typical CT findings of AIDS-related KS include bilateral ill-defined nodular opacities in a peribronchovascular distribution, which are also described as flame-shaped lesions [35, 36]. Areas of ground-glass attenuation surrounding one or more nodules, the so-called halo sign, have also been described [37, 38]. Nodules usually measure 1–2 cm in diameter and tend to coalesce [33, 34]. Areas of consolidation and ground-glass opacities separated from nodules also may be seen [37, 39]. Previous studies have shown that pleural effusions are present in 35–60% and lymphadenopathy (axillary, mediastinal, or hilar) in 33–53% of patients [35, 37, 39, 40]. The enlarged lymph nodes usually measure less than 20 mm in diameter [35]. Other common findings include peribronchovascular and interlobular septal thickening and fissural nodularity [37]. Larger masses and cavities may be seen but are less common [39]. Chest wall disease involving the sternum, ribs, thoracic spine, and subcutaneous tissue has been described [40].

The findings in our study concur with the radiologic findings in previous case reports of KS-associated immune reconstitution syndrome [16, 18, 19]. We found that patients with this syndrome have radiographic and CT findings similar to those of patients with AIDS-related KS without immune reconstitution syndrome. However, the incidence of pleural effusions and lymphadenopathy was higher than described for patients with AIDS-related KS without immune reconstitution syndrome. A notable difference was found in the follow-up of these patients. All patients in our series, except one who received chemotherapy, had marked progression of pulmonary abnormalities soon (mean, 16 days; range, 14–20 days) after the onset of immune reconstitution syndrome.

Therefore, rapid progression of pulmonary abnormalities on chest radiographs and CT

HAART. There was also associated worsening of herpes simplex and nontuberculous mycobacterial infection. CT showed an increase in the number and size of pulmonary nodules and adjacent ground-glass opacities. The patient's condition improved after chemotherapy.

The interval between initiation of HAART and development of immune reconstitution syndrome is variable [4, 9, 10, 28, 29]. Hirsch et al. [29] found the interval varied from less than 1 week to several months. In the series reported by Ratnam et al. [10], seven (14%) of 51 episodes of immune reconstitution syndrome in 44 patients occurred 24 weeks after HAART. Shelburne et al. [4] reviewed three cases of KS-associated immune reconstitution syndrome in which the intervals between HAART and symptoms were 3.6, 8.6, and 42.8 weeks. In our series, the interval between initiation of HAART and onset of pulmonary KS-associated immune reconstitution syndrome ranged from 1 to 22 weeks.

The radiographic and CT findings of AIDS-related KS are well described in the literature, but to our knowledge, except for a few case reports [16,
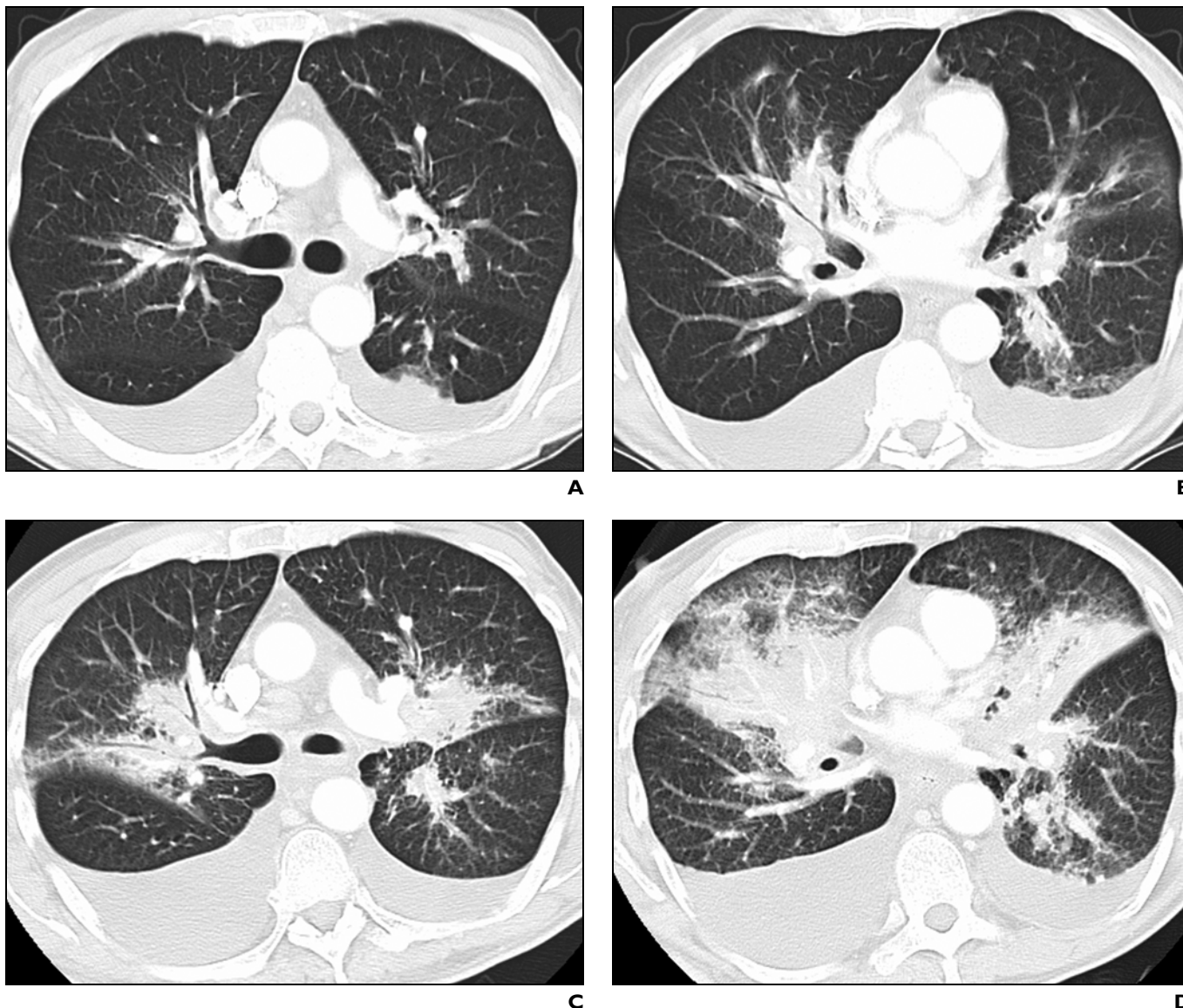
Fig. 4—59-year-old man with autopsy-confirmed Kaposi sarcoma–associated immune reconstitution syndrome.
A and **B,** CT scans (5-mm slice thickness reconstruction) at level of carina (**A**) and inferior pulmonary veins (**B**) show central peribronchovascular thickening and bilateral pleural effusion.
C and **D,** CT scans (5-mm slice thickness reconstruction) at level of carina (**C**) and inferior pulmonary veins (**D**) obtained 14 days after **A** and **B** show increase in peribronchovascular thickening and pleural effusion and development of bilateral perihilar consolidation.

scans in association with acute worsening of pulmonary signs and symptoms in patients who have recently started HAART does not necessarily indicate a diagnosis of infection. When radiologic findings are compatible with pulmonary KS, the possibility of KS-associated immune reconstitution syndrome should be considered, particularly in association with cutaneous or mucosal lesions compatible with KS. The diagnosis of this syndrome requires exclusion of other conditions that can cause similar findings, particularly *P. jiroveci* and

community-acquired pneumonia. Other differential diagnoses include drug toxicity and progression of disease not related to initiation of HAART. In the latter case, there is no temporal relation between initiation of antiretroviral therapy and the onset of the symptoms, and the viral load and CD4 cell count usually do not respond to HAART [14, 41].

As shown in previous reports of pulmonary KS-associated immune reconstitution syndrome [16, 18], bronchoscopy may be unrevealing, as it was in all four of our patients, in-

cluding the one whose autopsy showed extensive pulmonary KS. The main value of negative bronchoscopic findings is in excluding infection as a cause of clinical deterioration. Surgical lung biopsy can be performed if histologic diagnosis is necessary. However, because patients with immune reconstitution syndrome may have severe clinical deterioration, the risk-to-benefit ratio of open lung biopsy needs to be considered for each patient. If enough evidence of disseminated KS is proved by the presence of skin or mucosal le-

sions and if radiologic features are in keeping with pulmonary KS and infectious diseases have been excluded, surgical lung biopsy can be avoided. This scenario occurred in one of our cases: The patient received chemotherapy for disseminated KS without histologic proof of pulmonary KS, and all KS lesions, including the pulmonary lesions, were ameliorated.

The anecdotal nature of previous reports precludes firm recommendations regarding therapy. There are no guidelines regarding the continuation or interruption of HAART. Antiretroviral therapy usually is discontinued when inflammatory reactions are considered life threatening [29], as in the case of pulmonary KS-associated immune reconstitution syndrome. In the study performed by Bower et al. [8], despite initial deterioration, the condition of 10 patients with KS-associated immune reconstitution syndrome improved with continuation of HAART. None of those patients, however, had pulmonary involvement. The use of antiinflammatory agents, especially corticosteroids, is usually recommended for other immune reconstitution syndromes in severe cases.

Although the prognosis of KS-associated immune reconstitution syndrome is usually good [8], pulmonary involvement in patients with this syndrome seems to indicate a poor outcome, as shown in our cases and in previous reports [16–18]. The institution of chemotherapy can be beneficial to patients with pulmonary KS-associated immune reconstitution syndrome. In our small series the one patient who survived was the only one who received chemotherapy. The other three patients did not receive this treatment because of rapid clinical deterioration. The few cases reported in the literature had similar outcome [16–19]. The limitations of our study included its retrospective character, the small number of patients, and the lack of histologic and cytologic confirmation of pulmonary KS in three of the four patients.

In conclusion, although HAART is the mainstay of management of KS, a few patients experience worsening of KS during the first several months of therapy, and radiologists must be aware of the radiologic manifestations of pulmonary KS-associated immune reconstitution syndrome. The most common chest radiographic findings of this syndrome include ill-defined nodules, reticular and reticulonodular opacities, and consolidation with a predominantly perihilar distribution. Kerley B lines and pleural effusions also are common findings. The CT findings are ill-defined pulmonary nodules and peribronchovascular and interlobular septal thickening. Other common findings include the halo sign, consolidation, ground-glass opacities, nodular pleural thickening, lymphadenopathy, and pleural effusion. These abnormalities have a predominantly peribronchovascular distribution and may show marked progression in a short time.

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