Assessment of ground-glass opacity on a patient undergoing chemotherapy

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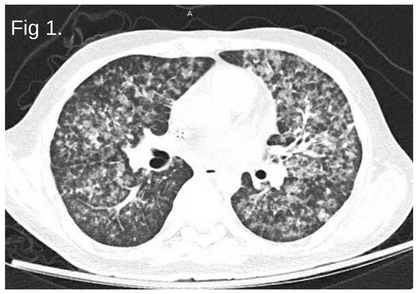
Case

A 31 year-old male with history of newly diagnosed Hodgkin's lymphoma presented with shortness of breath, persistent fever and seizure like activities. Initial CT scan revealed diffuse lymphadenopathy with normal lung parenchyma. After initiation of chemotherapy, patient developed hypoxia and diffuse centrilobular ground-glass opacity on CT scan (Fig.1). Initial evaluation including bronchoalvaloar lavage were unremarkable. Lung biopsy showed non-specific focal fibrosis (Fig. 2). However, further evaluation with immunohistochemistry revealed positive immunostaining for cytomegalovirus (CMV) (Fig. 3). CMV pneumonitis was confirmed with other supportive evidence with viral culture and high serum CMV PCR titer. After an appropriate therapy with Foscarnet, patient was able to wean from oxygen and subsequent CXR showed dramatic improvement after 1 week of treatment (Fig 4).

Fig 1.



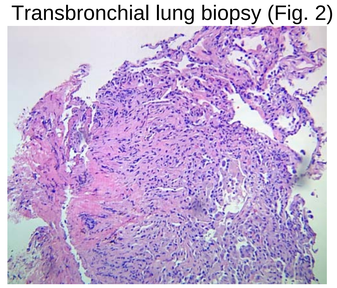
Blood culture	no growth
Urine culture	no growth
Wound cultures	Enterobacter Coloacae Enterococcus Faecalis
Quantiferon Gold Plus	(-)
HIV	(-)
HTLV I/II	(-)
EBV PCR	24600
Hep C Ab	(-)
Hep B sAg	(-)
Hep B sAb	positive (immune)

Bronchoalveolar lavage

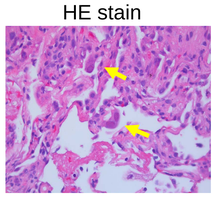
Gram stain	(-)
culture	no growth
AFB stain	(-)
culture	no growth
Beta-D Glucan	<31
Aspergillus PCR	(-)
PJP PCR	(-)

- GMS stain: No pneumocystis organisms or fungi.
- No foamy exudate or viral inclusions
- Cytology: Negative for malignant cells.

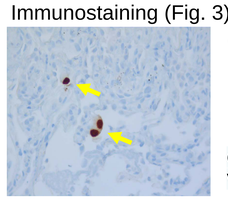
Transbronchial lung biopsy (Fig. 2)



HE stain



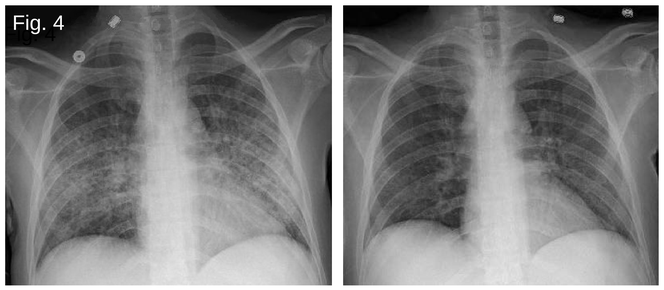
Immunostaining (Fig. 3)



CMV	positive
HSV	negative
HSV II	negative
EBER (ISH)	negative

CMV PCR	344,000
Viral culture	CMV positive

Fig. 4



After 1 week of treatment

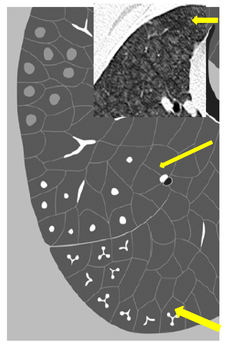
Differential diagnosis

Differential diagnosis of ground-glass opacity in patients undergoing chemotherapy are broad, including, but not limited to lymphangitic spread of tumor, infections, pulmonary edema, diffuse alveolar hemorrhage and drug toxicities. Detailed history and careful evaluations are warranted to guide our decision and an appropriate treatment.

Serologic evaluation for infection including CMV PCR, EBV PCR, Beta-D Glucan HSV, HZV titer, HIV and cultures should be sent as soon as suspected since they are easy to be obtained and could be monitored for treatment responses.

The patterns of ground-glass appearance (centrilobular vs crazy paving) on CT scan may guide the differential diagnosis.

Centrilobular patterns

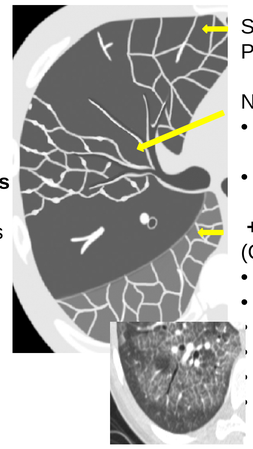


Ground-glass opacity
- **Hypersensitivity pneumonitis** (environmental, drugs)

Nodules
- **Infectious bronchiolitis** (bacterial, viral, fungal)
- Respiratory bronchiolitis
- Diffuse panbronchiolitis
- Miliary TB (random)
- Metastasis (random)

Tree-in-bud
- Mucus impaction

Interlobular septal thinking



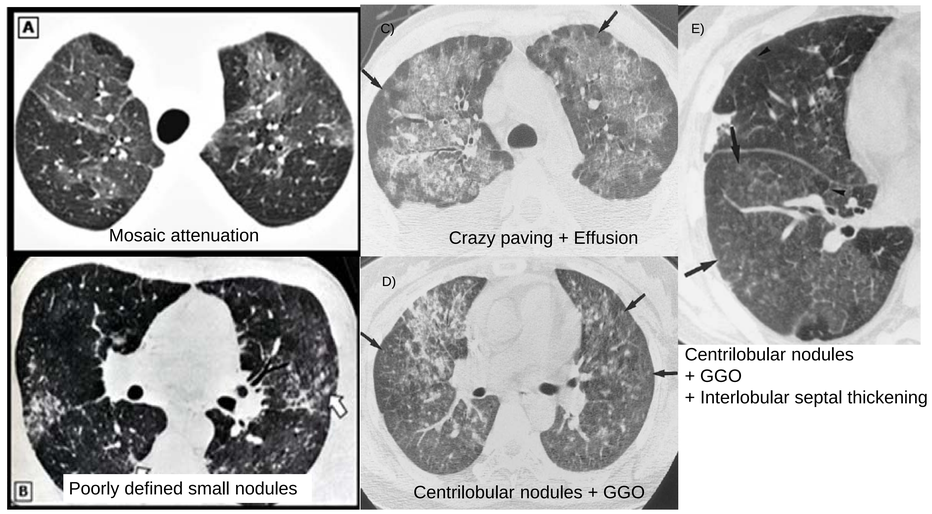
Smooth
Pulmonary edema

Nodular
- **Lymphangitic spread of cancer**
- Sarcoidosis

+Groundglass opacity
(Crazy paving pattern)
- Alveolar proteinosis
- **PJP pneumonitis**
- **Pulmonary edema**
- **Alveolar hemorrhage**
- Adenocarcinoma in situ
- Lipoid pneumonia

Patterns of CMV pneumonitis

CMV pneumonitis requires additional consideration as the CT findings are variable



Centrilobular nodules
+ GGO
+ Interlobular septal thickening

CMV pneumonitis

		Definition
CMV infection	Asymptomatic viremia	Virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen regardless of symptoms or signs
CMV disease		Evidence of CMV infection with attributable symptoms or signs
	CMV syndrome	Fever, malaise, weakness, myalgias, and arthralgias, leukopenia, thrombocytopenia without end-organ involvement
	CMV pneumonitis	Upper respiratory symptoms and tissue invasion

Symptoms
Low-grade fever, shortness of breath, nonproductive cough, and changes in measured pulmonary function

Diagnosis
1. Bronchoscopy with transbronchial biopsy
   - Identification of CMV inclusions (gold standard)
   - Positive CMV-specific immunohistochemistry staining
   PCR or culture in bronchoalveolar lavage (BAL) fluid may be just viral shedding not tissue-invasive disease.

2. Quantitative CMV PCR from blood
   CMV PCR results are often available prior to the biopsy results
   May influence the decision to initiate antiviral therapy.
   Important to establish the baseline viral load to monitor response to therapy.

Treatment
- IV Ganciclovir 5 mg/kg IV every 12 hours, with dose adjustment for renal dysfunction

Once the patient has demonstrated clear clinical improvement, IV ganciclovir can be transitioned to oral Valganciclovir.

- Foscarnet 60 mg/kg IV every 8 hours (severe disease or resistant CMV)
- Cytomegalovirus immune globulin (CytoGam)

Side effects
Ganciclovir:
Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, and bone marrow failure
Valganciclovir:
Granulocytopenia, anemia, thrombocytopenia, and pancytopenia
Foscarnet:
Nephrotoxicity

Conclusion

Timely bronchoscopy with possible transbronchial lung biopsy should be considered before further deterioration of clinical status.

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