The Mote in thy Brother's Eyes - Fusarium Solani in Leukemia Host

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Research Article

Keywords: Immunocompromise, Fusarium, Eye, Anti-fungal, Skin

Posted Date: November 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-787465/v1

Abstract

Fusariosis is increasingly seen among immunocompromised host. The organism is known for its virulence and spectrum of infections. Presenting here a case of relapse acute myeloblastic leukemia on chemotherapy with acute onset of red painful eye followed by widespread painful skin lesions. Microbiological and radiological investigations diagnosed her with disseminated fusariosis. Treatment was challenging in view its inherent resistance to multiple anti-fungal agents and the need for early aggressive source control. The case report reflects the importance of early diagnosis and combination chemotherapy to salvage the patient from high mortality.

Introduction

Fusarium spp. have been increasingly recognized in recent years as pathogens in immunocompromised hosts, causing a spectrum of localized, invasive and disseminated infections, with correspondingly higher mortality rates [1]. Immunocompromised hosts with prolonged and severe neutropenia are at risk of acquiring *Fusarium* spp. infections, despite increasingly broad anti-fungal prophylaxis [2]. It is crucial to recognize localized fusariosis early since treatment of disseminated disease is often ineffective, given its inherent resistance to most anti-fungal agents [3]. Combination therapy is generally recommended along with early aggressive surgical control of the site of infection where possible [4].

Case Report

We report the case of a 59-year-old female with acute myeloid leukemia who relapsed 2 years after achieving remission. She was initiated on salvage FLAG-Ida (fludarabine, cytarabine [cytosine arabinoside], granulocyte colony-stimulating factor, idarubicin), and prophylactic posaconazole as a bridge to allogeneic hematopoietic stem cell transplant (HSCT). Antimicrobial prophylaxis included trimethoprim-sulfamethoxazole, posaconazole, and acyclovir. On day 11 of chemotherapy (day 7 of neutropenia), the patient developed left eye pain and erythema, initially diagnosed as episcleritis by ophthalmology. She became febrile, with worsening left eye redness, and was treated with broad-spectrum antibiotics (intravenous (IV) piperacillin-tazobactam, then IV meropenem) for preseptal cellulitis (Fig. 1), which was localized without intra-orbital extension on a computed tomography scan of the orbits at that time. She was subsequently noted to have multiple tender nodular skin lesions on her extremities (Fig. 2) beginning from day 19 of chemotherapy. A skin biopsy showed invasive fungal hyphae, and eventually grew *Fusarium solani* (Fig. 3). *Fusarium solani* was also cultured from blood (Fig. 3). Only a single routine blood culture bottle was positive out of three sets taken on the same day,highlighting limited sensitivity of blood cultures for detection of disseminated fusariosis. Serum galactomannan was negative. Upon noting the skin lesions, she was started on a therapeutic dose of IV voriconazole, and later liposomal amphotericin (5mg/kg escalated to 10mg/kg) was added. She also underwent several local eye debridements for the interval development of left orbital cellulitis with episcleral abscess formation, which was demonstrated on magnetic resonance imaging. Intra-operative cultures also grew *Fusarium solani*. Her neutrophil count recovered on day 29 of chemotherapy and a day 35 bone marrow

examination showed morphological remission. Despite attempts at source control, aggressive anti-fungal therapy and count recovery, the patient continued to deteriorate clinically and radiologically (Fig. 4). She succumbed to disseminated fusariosis a month after she first experienced eye symptoms. The identification of *Fusarium* down to species level and the difficulty with interpretation of anti-fungal susceptibility (Table 1) testing further hinders effective treatment. This case also illustrates the failure of broad anti-fungal prophylaxis with posaconazole, which may result in more resistant, non-aspergillus mould infections.

Table 1
Anti-fungal drug sensitivity for *Fusarium solani* isolated from the patient's blood culture.

***Fusarium solani* susceptibility**	
Amphotericin B	2 mg/L
Voriconazole	> 8 mg/L
Anidulafungin	> 8 mg/L
Posaconazole	> 8mg/L

Discussion

Fusarium spp. are environmental filamentous fungi abundantly present in soil, plants and water [5]. There are more than 300 species of *Fusarium*, and most are harmless. Some exist on the skin as a member of skin flora, while others can cause broad spectrum infections depending on the host immune status. They have the ability to produce mycotoxins that suppress cellular and humoral immunity and cause tissue breakdown [10], resulting in invasive disease. *Fusarium solani* species, as the most virulent, is also the most common (approximately50% of cases) in causing invasive disease followed by *Fusarium oxysporum* and *Fusarium fujikuroi* species (approximately20% each) [1]. In immunocompetent hosts, localized skin infection and keratitis are the most common sites of infection [11]. Immunocompromised hosts can acquire *Fusarium* spp. in the hospital setting via airborne inhalation of fusarial conidia including from contaminated hospital water systems, or dissemination from their own benign skin or nail infections, or from some other site which can lead to invasive disseminated disease. [12]

Patients with hematological malignancies, particularly those undergoing induction chemotherapy or HSCT in the first 30 days post-transplant are most susceptible to IFI, including invasive fusariosis, due to profound defects in cellular and humoral immunity. In study done in the United States, the incidence of fusariosis among acute myeloid leukemia patients was less than 1 percent [13]. On the other hand, a Brazilian study found that fusariosis had the highest one-year cumulative incidence amongst IFI in

patients with acute myeloid leukemia (AML), myelodysplasia (MDS) or HSCT (23 out of 937 patients) [14]. Therefore, geographical variations seem to play a role as well and must be taken into account while managing such patients. In Brazil, *Fusarium solani* species is the dominant type, whereas in some European countries' *Fusarium fujikuroi* species complex is the most common [15].

Histopathological differentiation of *Fusarium* spp. from other hyaline hyphomycetes such as *Aspergillus* spp. may be difficult [6], as both appear as non-pigmented, septated hyphae with acute angle branching. Species identification can be difficult but matrix-assisted laser desorption/ionization time of light (MALDI-TOF) can identify the species type correctly. In terms of serum fungal markers, serum galactomannan can be positive even before the first clinical manifestation of invasive fusariosis [7]. Serum 1,3-β-d-glucan may also be positive in invasive fusarial infections. However, 1,3-β-d-glucan (BG) is a common antigen in various other fungal organisms and will not distinguish fusariosis from other fungal infections such as Candida, Aspergillus or Trichosporon infections. It can also be elevated by other factors such as hemodialysis with cellulose membranes and exposure to certain certain intravenous antimicrobials [8]. Elie Azoulay et al assessed the contribution of BG to the diagnosis of invasive fungal infections (IFI) among 737 patients with underlying hematological malignancies admitted to the intensive care unit (ICU). IFI was documented in 78 patients and only 3 had *Fusarium* spp. infections. BG concentration was higher in patients with IFI compared to those without IFI. At a BG cutoff of 80 pg/mL, the sensitivity and specificity were 72% and 65% respectively, while negative and positive predictive values were 94% and 21% respectively assuming prevalence of 10%. [9]

Localized fusarium infections can be managed with surgical intervention and topical anti-fungal agents. As the skin is commonly the source of subsequent dissemination, early aggressive intervention reduces the bulk of the disease and controls it. Disseminated infection mandates the use of anti-fungal agents in addition to surgical control whenever amenable. *Fusarium* spp. are known to have high in vitro resistance to most anti-fungal agents. However, varying susceptibility patterns are seen between different *Fusarium* spp. [16, 17]. *Fusarium solani*, isolated in our patient, is usually resistant to azoles and tend to have higher minimum inhibitory concentration (MIC) to amphotericin B compared to other *Fusarium* spp. [18]. There is no clear consensus for treatment of IFI due to fusarium and no solid recommendations are available. A report of 84 patients with hematological disease and invasive fusarium infection who were treated with different amphotericin B types (13 patients with liposomal amphotericin Band 69 with amphotericin B deoxycholate) found that 32% responded to treatment but the 90-day mortality was high with only 21% alive by that time point [19]. Furthermore, a recent international multi-centered retrospective review of invasive *Fusarium* infection, in which 84% of the 88 patients included had hematological malignancies, found no correlation between the MIC of the *Fusarium* spp. and mortality at 6 weeks after IFI [20]. Most patients in that study were treated with either voriconazole monotherapy or a combination of voriconazole and amphotericin B.

Due to the high intrinsic anti-fungal resistance and limited availability of susceptibility testing, many clinicians will give combination anti-fungal treatment for patients with disseminated fusariosis. However, little clinical data is available for this practice, and this is mainly in the form of case reports. Durand-Joly

et al. presented a patient with fever, neutropenia and necrotic skin lesion on her calves on day 6 of induction chemotherapy for acute lymphoblastic leukemia (ALL). Despite being on liposomal amphotericin B, she was persistently febrile and failed to clear blood cultures until voriconazole was added to the treatment regimen [21]. A case report by Rothe et al. described a patient with disseminated *Fusarium oxysporum* following chemotherapy for AML who failed to show response to amphotericin B deoxycholate until oral terbinafine was added. She responded successfully by day 13 of combination therapy [22]. Case reports can be biased, but given the general rarity of IFI due to *Fusarium* spp., it is difficult to conduct prospective trials.

Prevention of IFI in hematology and HSCT patients during the neutropenic phase is essential, and includes placing high risk patients in positive pressure rooms with high-efficiency particulate air (HEPA) filters and avoiding contact with potential reservoirs of *Fusarium* spp. such as fresh fruit and plants, and in some cases tap water [23]. In addition, anti-fungal prophylaxisduring induction chemotherapy in high-risk hematology patients and allogenic HSCT recipients, has shown promising results in preventing IFI [24].

Unfortunately, anti-fungal prophlaxis is not universally effective, and breakthrough infections, such as that seen in our patient, have been reported. A retrospective study by Auberger et al. assessed for breakthrough invasive fungal infections (bIFI) in 95 high risk patients who received primary prophylaxis with posaconazole 200mg three times a day. IFI was defined as a breakthrough if fungal infection occurred 4 days or more after initiation of posaconazole. The incidence of bIFI was 13% overall, out of which 41% were proven bIFI and 59% were probable bIFI. Of the proven bIFI, 55% were *Mucor* spp. and 45% were yeast (*Candida* spp.). [25]

Another retrospective study by Lerolle et al. evaluated the incidence of bIFI in 270 hematology patients who received at least 7 days of primary anti-fungal prophylaxis with posaconazole. 6 patients had proven bIFI and 3 had probable bIFI, for an overall incidence of 3.3% bIFI. Out of these 9 bIFI, 2 had candidemia (*Candida glabrata*), 3 had pulmonary aspergillosis, 2 had pulmonary mucormycosis and 2 had disseminated fusariosis [26]. These two retrospective studies, while having disparate rates of bIFI in patients on posaconazole prophylaxis, found manyfungal infections caused by emerging pathogens other than *Candida albicans* and *Aspergillus* spp. These studies, albeit limited, provide evidence that clinicians need to have a high index of suspicion for IFI in such patients even if they are on anti-fungal prophylaxis, especially those who continue to be febrile despite broad-spectrum anti-bacterials or those who develop suspicious manifestations in the setting of prolonged neutropenia. Larger studies from multiple centers are required to determine the true rate of bIFI in high-risk hematology and HSCT patients receiving anti-fungal prophylaxis with mold-active azoles.

What is unusual about our case is that she had progressive dissemination and demise despite recovery of her neutrophils. Most studies have shown that the main risk factors for mortality are persistent neutropenia with persistent disease or ongoing use of corticosteroids [19, 23], none of which was present

in this case. It is likely that she already had widespread dissemination before her neutrophils recovered, and the burden of this resistant fungal infection was too high for her immune system to clear.

In conclusion, hematology patients undergoing high risk chemotherapy and receiving broad anti-fungal prophylaxis, remain susceptible to IFI. Every effort should be made to diagnose IFI, particularly fusariosis, in these patients due to the high associated mortality.

Declarations

Conflict of Interest:

Not applicable

Funding:

Not applicable

Availability of data and material:

Not applicable

Code availability:

Not applicable

Ethics approval:

Not applicable

Consent to participate:

Not applicable

Consent for publication:

Consent taken from daughter of patient. As the case report was written after patient's demise

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Figures

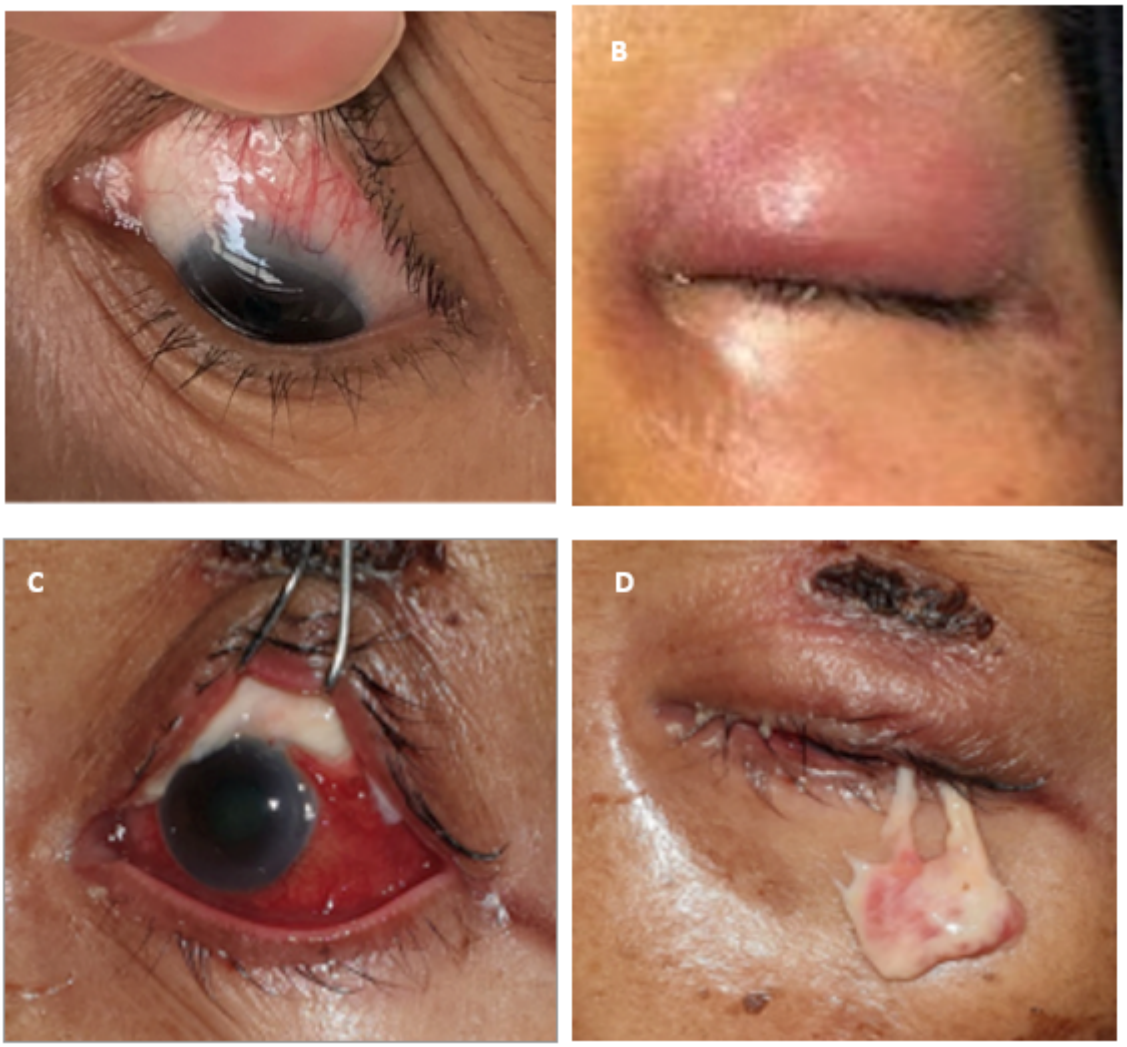

Figure 1

Progression of eye symptoms over the course of illness. A. Day 1 of symptoms. Initial impression is that of episcleritis. B. Day 6 of symptoms – worsening orbital cellulitis despite broad spectrum anti-microbial therapy. C and D. Day 23 of symptoms.

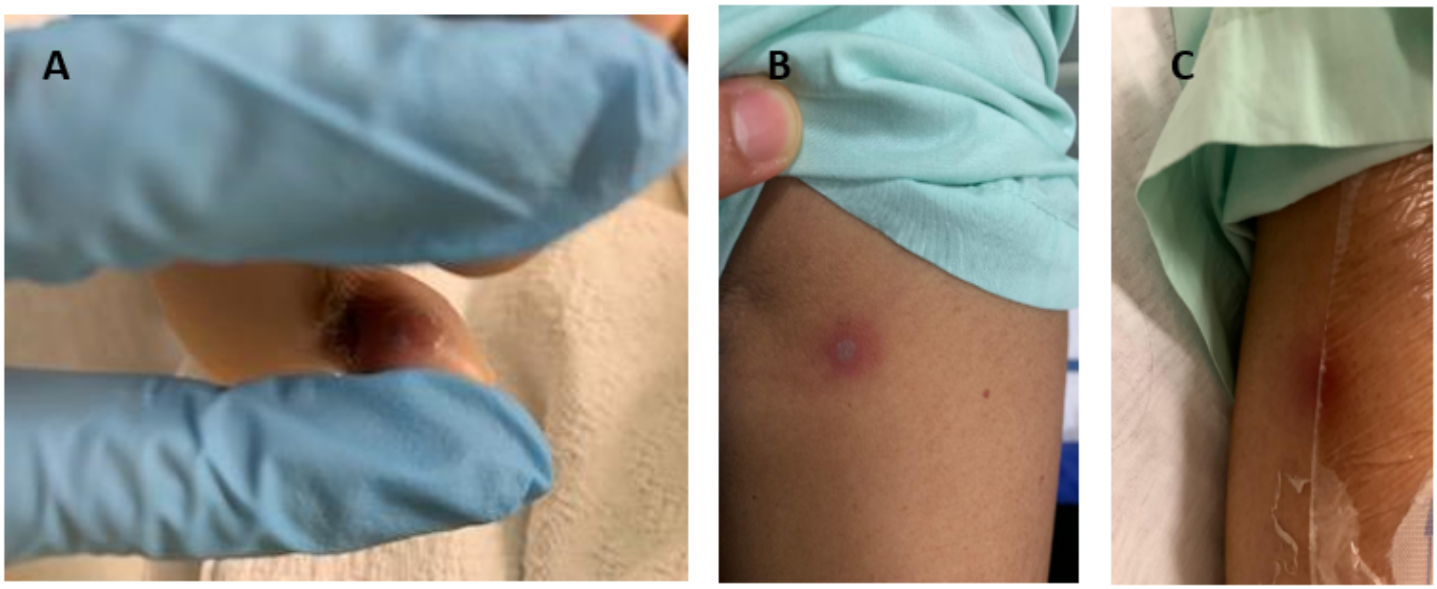

Figure 2

Multiple skin lesions. A. Left fifth toe. B. Left arm. C. Right calf.

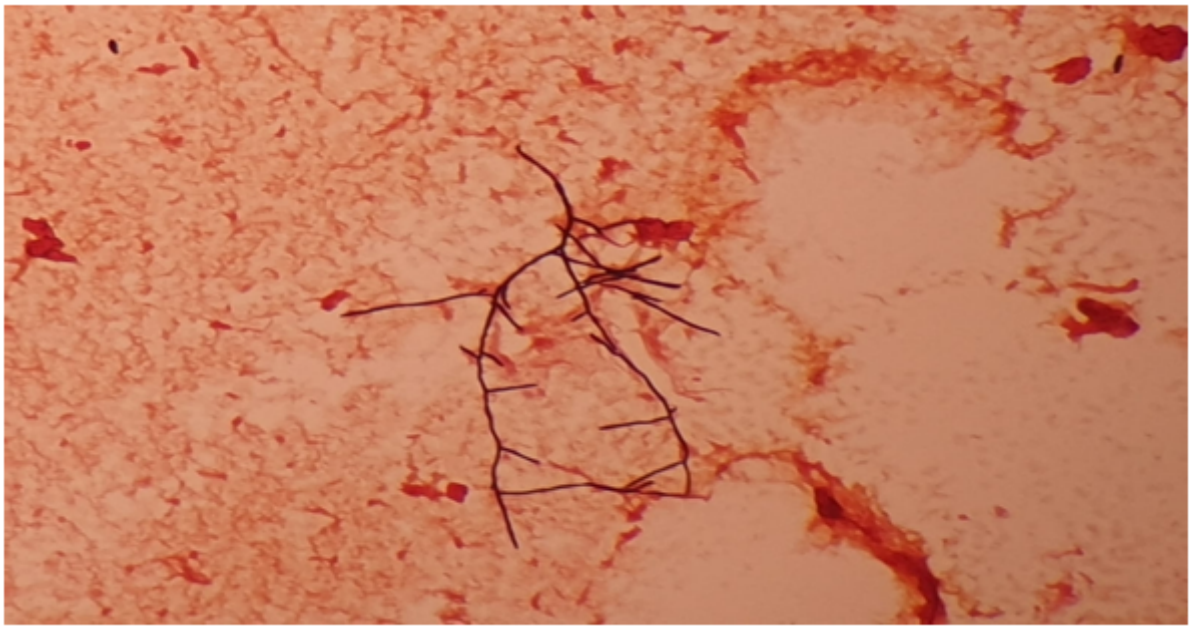

Figure 3

Gram stain from blood culture bottle demonstrating fungal hyphae

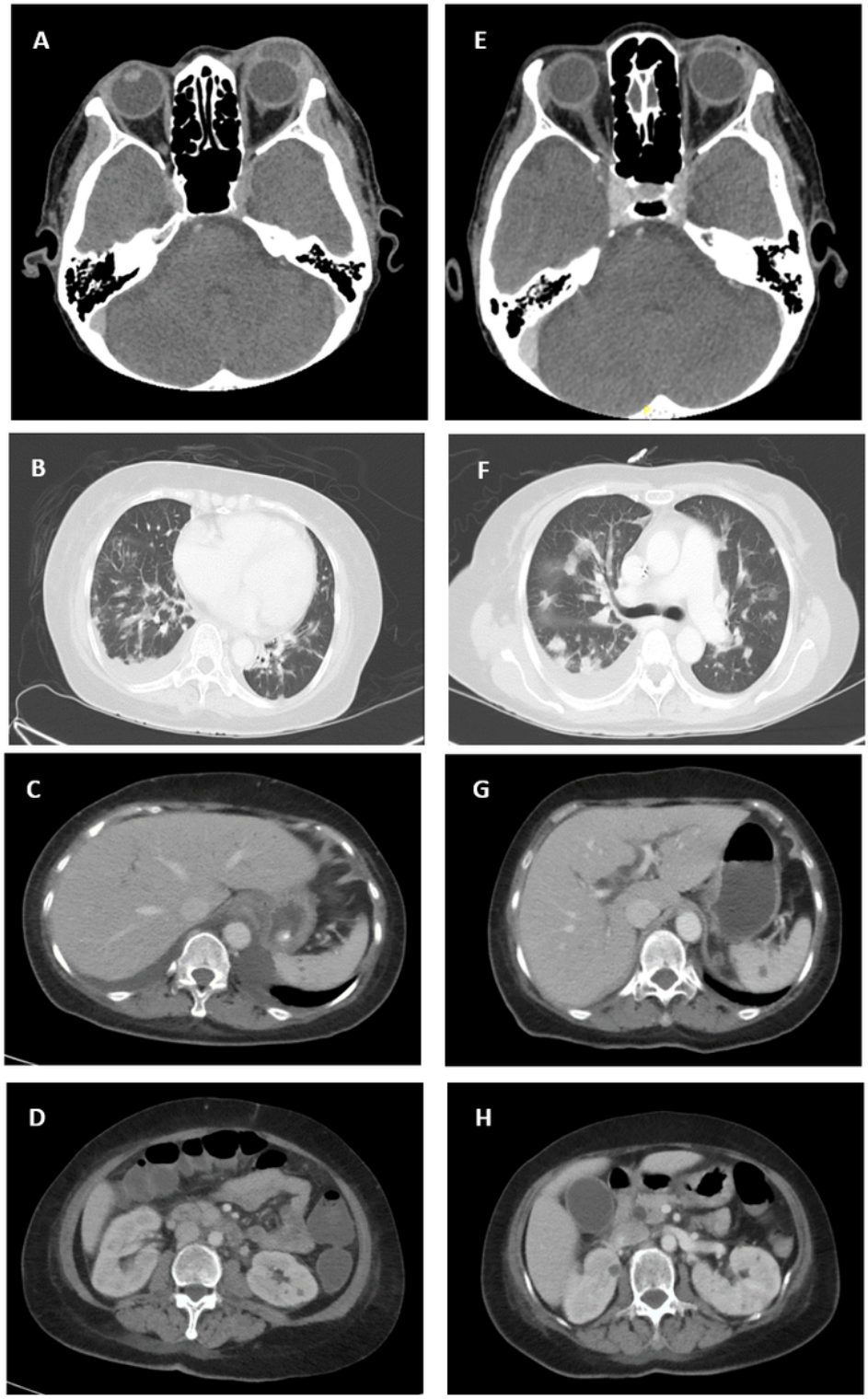

Figure 4

Worsening radiological signs. A. CT orbit on Day 12 of symptoms show an abscess in the left superoanterior episcleral region. B-D. CT thorax, abdomen and pelvis Day 19 of symptoms shows multiple bilateral air space opacities in the lungs, and multiple abscesses in the liver, spleen and kidneys. E. CT orbits on Day 24 show a recurrent left eye collection and a new right eye collection abutting the

rectus muscle. F-H. Repeat CT thorax, abdomen and pelvis on Day 29 shows worsening air space changes in both lungs and increase in size and numbers of abscesses in the liver, spleen and kidneys.