Learning objectives

The purpose of this paper is to present the role of the radiologist in the emergency department in the approach of chemotherapy-induced febrile neutropenia.

This paper discusses several diagnostic imaging modalities such as plain radiography, ultrasonography and computed tomography, diagnostic tools frequently used in this setting to detect complications.

Abbreviations:

TC: CT.

IV: Intravenous.

Background

Definition of febrile neutropenia.

Fever in a neutropenic patient is considered a medical emergency. In the pre-antibiotic era, three out of four chemotherapy-related deaths were due to infections. With the advent of broad-spectrum antibiotics have been able to implement more aggressive chemotherapy regimens.

Neutropenia is defined as absolute neutrophil count < 500 cells / cubic millimeter (calculated by multiplying the total number of leukocytes and percentage of neutrophils rabbles). In a neutropenic host, neutropenic fever is defined as a temperature measurement of > 38 °C sustained for more than one hour or an isolated measurement of > 38.3 °C.

Due to the attenuated inflammatory response in these patients, the signs and symptoms of infection may be minimal, to the point that someone may be afebrile despite suffering a serious infection, especially the elderly or those receiving corticosteroids. In clinical practice it is essential to have a high index of suspicion of occult infection, even in the absence of fever, the presence of hypothermia, hypotension or clinical deterioration, situations that indicate an early start empirical antibiotics.
Pathogenesis of febrile neutropenia.

Contributing factors to the pathogenesis can be divided into those related to chemotherapy and and those factors associated with primary malignant tumor.

Chemotherapy has two major effects: first, its myelotoxicity (reducing neutrophil counts and inducing defects in chemotaxis and phagocytosis) and second, the mucositis along the gastrointestinal tract, that serves as a nest of local infection or point of entry for systemic infection by endogenous flora, which incidentally, is the cause of most febrile neutropenic episodes. The lymphatic obstruction in the bronchial tree, gastrointestinal tract or urinary tract by the tumor or surgery also cause infection.

The primary neoplasm has additive immunosuppressive effects. It is known that there are alterations in the neutrophil function in cancer patients before initiation of chemotherapy.

It is possible to identify the source of infection in approximately 30% of episodes of febrile neutropenia. A more common scenario is a bacteremia as the only evidence of infection, which can be documented in about 25% of patients (to a lesser extent some patients may show fungemia). Approximately 80% of infections with identified agent, originate from the endogenous flora. Among the pathogens involved, the largest group is made up of bacteria (gram positive isolates three times more frequent than gram negative), followed by fungi (Candida albicans, Aspergillus, Mucor) and virus (specially human herpes virus).

Imaging findings OR Procedure details

Diagnostic imaging.

A basal chest X-ray should be obtained as part of the initial evaluation of these patients, even in absence of respiratory symptoms. If the X-ray was not conclusive would be quickly followed by a chest CT. The thoracic imaging test would be repeated if the respiratory symptoms persist or worsen.

The findings on plain film are often subtle or even absent in patients with pneumonia and abnormalities may become more evident in parallel to increased symptoms and especially during the resolution of neutropenia.

The chest CT findings may show findings as pneumonia or pulmonary nodules in patients with normal plain film. In one study, CT showed pneumonia in more than half of a
group of neutropenic patients that showed normal chest X-ray and persistent fever. It was concluded that the TC could establish the diagnosis five days before radiography, although this did not translate into improved clinical outcomes.

Although the TC has not demonstrated change clinical outcomes, it should be a low threshold for its implementation in presence of respiratory symptoms. This imaging modality help in guiding selection and duration of antibiotic and can help ruling out invasive pulmonary mycosis.

If clinically indicated, a CT of another organs must be done (skull, sinuses, abdomen / pelvis).

**Radiological manifestations of infections in febrile neutropenia.**

After blood infection as bacteremia or fungemia, the most common source of infection in neutropenic patients with fever is found in the respiratory tract (sinuses and lungs).

Prolonged neutropenia is associated with severe sinus infections, especially fungal etiology, as is the case of acute invasive fungal rhinosinusitis, a rapidly progressing infection with mortality rates between 50 and 80%. The organisms most frequently involved are Aspergillus species and Zygomycetes such as Mucor.

The CT shows thickening and hypoattenuation of the sinus mucosa or an intraluminal soft-issue attenuation area. There is a predilection for unilateral sphenoid or ethmoid involvement (Fig. 1 on page 6 and Fig. 2 on page 7). It associates an aggressive bone destructive process that occurs rapidly and extends the inflammatory process to intraorbital and intracranial compartments. As these organisms spread through the vessels, it may have extrasinusal extension with intact bony walls. The intracranial extension from the sphenoid sinus leads to cavernous sinus thrombosis and invasive carotid affection with cerebral ischemia or fatal bleeding. There may be subtle leptomeningeal enhancement in the initial stages until cerebritis with brain abscess formation with the progress of the infection (Fig. 3 on page 8, Fig. 4 on page 9 and Fig. 5 on page 10). While CT is superior to assess bone involvement, MRI is better to identify the orbital and intracranial involvement, so this test would be conducted in a deferred but urgently. Treatment includes rapid surgical debridement and systemic antifungal therapy.

Angioinvasive pulmonary aspergillosis is a serious complication of deep and prolonged neutropenia. Aspergillus hyphae invade and occlude the pulmonary arteries of small-medium caliber leading to the formation of necrotic-hemorrhagic nodules or peripheral
hemorrhagic infarctions of trapezoidal morphology (similar to those associated with pulmonary embolism). Clinical diagnosis is difficult and the mortality remains high.

The chest radiography shows ill-defined nodules that may coalesce at the beginning of the infection (Fig. 6 on page 11). The CT findings include nodules surrounded by a "ground glass" halo and peripheric trapezoidal areas of consolidation, corresponding to hemorrhagic pulmonary infarcts (Fig. 7 on page 12, Fig. 8 on page 13, Fig. 9 on page 14 and Fig. 10 on page 15). In a patient with profound neutropenia, the halo sign is highly suggestive of the diagnosis, although it may be present in various diseases and other clinical settings. The separation of fragments of necrotic lung parenchyma is observed like the air crescent sign (similar to that of mycetoma) and is seen in the recovery phase of angioinvasive aspergillosis, coinciding with resolution of neutropenia. The treatment of this condition requires a systemic antifungal scheme of a relatively long duration.

The gastrointestinal tract is the seat of mucositis of varying degrees of severity. Candida spp. or human herpes virus (herpes simplex, cytomegalovirus) esophagitis is seen with some frequency, a condition with poor representation in the emergency radiology, except in cases of associated perforation or fistula. The diagnosis is essentially clinical and aided by evidence of oral candidiasis.

Less frequently, these patients may present typhlitis and perianal cellulitis. The typhlitis is a special type of neutropenic enterocolitis with predilection for cecum involvement, but sometimes affects ascending colon and distal ileum.

The TC shows circumferential thickening and distension of the cecal wall, which can show low attenuation because of edema and often pericecal fat stranding (Fig. 11 on page 16). Detection of complications like pneumatosis, pneumoperitoneum or pericolic fluid collections require urgent surgery (Fig. 11 on page 16, Fig. 12 on page 17 and Fig. 13 on page 18). In absence of the latter, the condition resolves with antibiotics and recovery from neutropenia. The CT is also useful for monitoring therapeutic response and indicate the need for surgery (eg, appearance of intramural air).

Another complication that can occur in these patients during recovery from neutropenia is hepatosplenic candidiasis. During periods of profound neutropenia intestinal mucosa may be invaded by Candida spp. and eventually infect the liver via portal. Some patients remain neutropenic and will die by a devastating infection despite treatment; in others, neutropenia and infection resolved favorably; and in the rest of them, the neutropenia resolved after candidiasis spread and the resulting response against infection will lead to multiorgan dysfunction. This inflammatory response determines the clinical and radiological picture.

The CT has a sensitivity of 90% and typically shows scattered multiple rounded lesions of small size and low attenuation value in hepatic and splenic parenchyma (Fig. 14
on page 19 and Fig. 15 on page 20). Sometimes involvement of the kidneys is associated. Ultrasound can also reveal these focal lesions but with a lower sensitivity (around 75%). Treatment consists of systemic antifungal administration but the outcome is often fatal. The implementation of antifungal prophylaxis in myelosuppressed patients has decreased the incidence of this serious infectious event.

Finally, an infection that can occur in neutropenic patients is fungal pyomyositis by saprophytic species of fungi (such as Fusarium species); microorganisms that are not hazardous to the immunocompetent host but take an invasive behavior in situations of profound neutropenia.

Pyomyositis consists of a primary muscle abscess that can be detected by ultrasound in two phases: an early, with poorly defined phlegmonous changes inside the muscle with hypoechoic areas (Fig. 16 on page 21) and a later with intramuscular fluid collection corresponding with abscesses (Fig. 17 on page 22). Similarly, these changes can be assessed in CT as hypoattenuating areas and intramuscular hypodense collection with peripheral enhancement, respectively for phases of phlegmon and abscess.

**Treatment.**

In every febrile neutropenic patient is urgent to begin empiric antibiotics adjusted for renal and hepatic function as soon as possible.

The main contribution of the radiologist in the emergency department is the accurate diagnosis of the site and type of infection; the impact is to guide the etiology in some cases leading to addition of antifungal treatment, withdrawal of indwelling catheters or surgical consultation as well as the performance of image-guided percutaneous drainage.

Thus, the early start of appropriate treatment for the site, type and microorganisms causing the infection, significantly reduces mortality.

**Images for this section:**
Fig. 1: A woman of 44 years-old with allogeneic bone marrow transplantation for lymphoma nasal T / NK with fever, headache and sinus symptoms with neutropenia. The contrast-enhanced CT of brain shows occupation of the sphenoid sinus and ethmoid cells with soft tissue attenuation material (arrow).
**Fig. 2:** In the same patient of Fig. 1, the CT of the brain with bone window settings shows ethmoid sinus occupation with erosion of bone cells (arrow).
Fig. 3: In the same patient as in Fig. 1, the contrast-enhanced CT of the brain shows a hypodense area with undefined borders in the basal part of both frontal lobes (*) compatible with cerebritis.
**Fig. 4:** In the same patient as in Fig. 1, another CT was performed two days after, because of clinical and neurological worsening shows extent of parenchymal involvement to both gangliobasal regions (arrows).
**Fig. 5:** The same study of Fig. 4 after administration of IV contrast shows a big hypocaptant area of cerebritis extending beyond the frontal region. This patient died hours later.
**Fig. 6:** A man of 81 years-old with profound neutropenia related to myelodysplastic syndrome that was admitted for severe pneumonia. The chest radiograph shows at least two nodular opacities of ill-defined borders in the lung parenchyma, one in the right upper lobe (curved arrow) limited inferiorly by the minor fissure and another in the right lung base (straight arrow).
**Fig. 7:** In the same patient as in Fig 6, the contrast-enhanced CT of the chest with mediastinal window shows a nodule (long arrow) in the right upper lobe and an associated infracarinal adenopathy (*). There’s also a smaller nodule in the apical segment of the lower lobe (short arrow) and a mild right pleural effusion.
Fig. 8: The same study of Fig. 7 with lung window settings shows a cavitated nodule with undefined borders and apparent pleural implantation base in the right lower lobe (*). This lesion is surrounded by a halo with "ground glass" attenuation. There’s also a small nodule with undefined borders in the left lower lobe (arrow) and right pleural effusion. In this case an invasive Aspergillus infection was confirmed and the patient improved after prolonged antifungal therapy.
**Fig. 9:** A man of 79 years-old with idiosyncratic agranulocytosis after surgery for inguinal herniorrhaphy. In the postoperative he required intubation and transfer to intensive care for severe sepsis. The contrast-enhanced CT of the chest with lung window settings shows a peripheric nodule in the left upper lobe with halo sign (arrow). There are moderate bilateral pleural effusion, a esophageal tube and a central venous catheter in superior vena cava.
**Fig. 10:** In a lower axial cut of the same study as in Fig. 9 there are two peripheral nodular lesions with associated halo sign in the right upper lobe similar to the contralateral one in the Fig. 9 (arrows). These findings corresponded to invasive aspergillosis and the patient improved with antifungal therapy.
Fig. 11: A woman of 55 years-old with neutropenia after chemotherapy for breast cancer admitted for fever, abdominal pain, vomiting and diarrhea. The contrast-enhanced CT of abdomen shows thickening and decreased enhancement of the cecum wall with intraparietal air because of pneumatosis (straight arrow). There are associated mesenteric fat stranding as well as extension of the gas dissecting pericecal area through the muscles of the anterior abdominal wall (curved arrow) and air in the mesenteric veins (*). The patient underwent intestinal resection and was discharged after a long hospital stay.
**Fig. 12:** In the same patient and study as in Fig. 11 in a lower pelvic level there's gas extending in the right parametrium (arrow).
**Fig. 13:** In the same patient and study as in Fig. 11 the contrast-enhanced CT of the upper abdomen shows air at the periphery of the liver parenchyma (arrow) with regard to pneumatosis portal.
Fig. 14: A woman of 20 years-old with profound neutropenia after chemotherapy instituted for relapse of acute lymphatic leukemia. She was admitted for febrile syndrome. The contrast-enhanced CT of the abdomen shows multiple small hypocaptant foci scattered in hepatic and splenic parenchyma.
Fig. 15: In the same patient and study as in Fig. 14 the lower axial cuts continue to show extensive hepatosplenic involvement. This patient did not respond to treatment and died three months later.
Fig. 16: A woman of 45 years-old with neutropenia after chemotherapy for non-Hodgkin lymphoma who complains of pain and swelling in her right thigh. The ultrasound of the thigh in a longitudinal scan shows a heterogeneous area (delimited with +) inside the rectus femoris muscle (*) with poorly defined hypoechoic images with regard to phlegmonous inflammatory changes.
Fig. 17: In the same patient as in Fig. 16, a cross section ultrasound of the thigh shows an irregular and hypoechoic lesion (arrows) within the rectus femoris muscle belly. These findings are consistent with an abscess.
Conclusion

Febrile neutropenia is a medical emergency, the outcome depends on early and appropriate treatment.

The increasing use of aggressive chemotherapy schemes with a parallel increase in the incidence of severe neutropenia requires that radiologists know their wide range of potential complications and diagnostic imaging. The radiologist is responsible for selecting the most appropriate sequence of imaging tests to identify the location of the infection and thus guide appropriate selection of antibiotic regimen.

References

1. Robbins GK. Fever in the neutropenic adult patient with cancer. [Internet Monograph]. UpToDate; 2012 [accessed January 24 2012]. Disponible en:


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