



Infections in Patients with Solid Tumors

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Introduction

Cancer patients represent an interesting challenge from the infectological point of view. Although patients with solid tumors do not have the same risk of infections as patients with oncohematological tumors, some predisposing factors can influence their evolution. These factors include tumor growth, malnutrition, alteration of anatomical barriers, and the adverse effects of various treatments.

Anatomical effect of tumors

Patients with large tumor masses may constitute a risk category for the development of infections.

Rapidly growing head and neck tumors can cause distortion or obstruction of the upper airway, which will require a tracheostomy. Tracheostomized patients have a higher risk of respiratory complications such as bronchitis or pneumonia since most of them have the respiratory system colonized with different microorganisms. On the other hand, patients with lung neoplasms are more likely to suffer from what is known as post obstructive pneumonia.

Patients with esophageal cancer are complicated by fistulas that can be esophagocutaneous or esophago-tracheal. The latter is observed in 5-10% of them and are the ones that offer the greatest

problems, being a frequent cause of aspiration pneumonia as a consequence of aerodigestive communication.

Gynecological or urinary tract tumors often cause obstruction or alteration in the urinary tree. This results in stasis and/or urine reflux thus increasing the risk of urinary infections.

Added to this is the fact that some patients require the placement of devices to unclog the urinary system such as double j catheters or nephrostomies, and others require indwelling urinary catheterization or intermittent catheterization. In each particular case, the indication for antibiotic treatment for each episode, or the decision for prophylactic antibiotic treatment, should be prioritized.

The complication associated with rapidly growing intra-abdominal tumors is necrosis and abscess, causing prolonged fever. In this case, the benefit of combined medical and surgical treatment will have to be evaluated.

Skin and soft tissue tumors also suffer this type of complication, generating large masses that ulcerate and become necrotic. This leads to colonization with multiple microorganisms and subsequent infection. In these cases, deformation, bleeding and bad smell are causes of social isolation.

Patients with breast cancer who underwent surgery with lymph node dissection suffer from lymphangitis, altering lymphatic drainage. These patients suffer cellulitis of the upper limbs ipsilateral to the tumor more frequently than the normal population.

Treatment effects

1. Effects of radiation therapy:

- **Head and neck:** in this area, the radiation treatment can result in distortion of the airway, associated with edema of the compromised tissues. Lymphatics and vasculature can also be obliterated. In soft tissues, this can manifest as swelling and redness of the affected area clinically simulating an infection, and the alteration in the vasculature and lymphatics favors it.
- **Lungs:** pulmonary fibrosis secondary to radiation therapy is common. In these cases, physical examination of the patients reveals the fine "velcro-like" crackles characteristic of fibrosis. Changes can also be seen on the chest x-ray. Therefore, the antecedent is important in these cases to rank it before a respiratory exacerbation.
- **Gastrointestinal system:** the intestine is very vulnerable to radiation causing the so-called actinic enteritis. This results from vascular injury and progressive ischemia, and the factors involved in its appearance are the fraction of the daily dose, the total dose administered and the volume of tissue included in the field to be irradiated.

Most symptoms are self-limited and disappear when treatment is complete. Chronic complications are seen months after radiation therapy is complete and can result in intestinal obstructions, perforations, bleeding, and fistula formation. Treatment is surgical in 2-17% of cases and is generally associated with the radiant treatment of gynecological, urinary, and rectal tumors. The patients with the greatest predisposition to suffer actinic enteritis are those with a history of abdominal surgeries and those undergoing simultaneous chemotherapy with drugs such as 5-fluorouracil. They have a greater predisposition to suffer invasive infections since there is an alteration of one of the mucosal barriers of the greater surface.

- Genitourinary system: actinic cystitis is also a frequent entity among patients who receive radiotherapy in the bladder area. Symptoms mimic those of a urinary tract infection, and cultures are always negative. There may even be hematuria.

- Osteo-radionecrosis: during the radiant treatment of malignant tumors, normal cells are also damaged. Non-tumor cells are heterogeneous in their origin and their sensitivity to radiation.

In descending order are tumor cells, endothelium, fibroblasts, muscle tissue, and nerves. This entity is the most serious complication of radiotherapy and the incidence varies between 10-15%, the mandible being the most frequent location. Physiologically, there is a decrease in the number and caliber of blood vessels. The sequence in the development of osteoradionecrosis is radiation, formation of hypoxic-hypocellular-hypovascular tissue and tissue destruction. One of the complications of this disease is infection. The tissues are permanently exposed, they are colonized and the loss of the regeneration and repair capacity of these lesions favors infection, and also facilitates their dissemination. Another associated symptom is the bad smell associated with the presence of anaerobic microorganisms.

- Skin and soft tissues: the alteration in the architecture of the skin tissues generated by radiation therapy leads to problems in the healing of the tissues.

Normal healing includes three phases: the inflammatory phase, the proliferation phase, and the maturation phase.

These patients not only have altered skin structure but other factors associated with treatment such as chemotherapy drugs and corticosteroids are added. Therefore, the evolution of surgical procedures in these patients may be affected by the alteration in healing caused by the treatment of the underlying tumor.

2) Effects of chemotherapy

Patients exposed to chemotherapy are subject to multiple organ damage. These patients should perform a thorough history and a thorough pretreatment physical examination to determine the underlying

clinical status. A list with all the drugs that the patient has received, the time they received them and the doses of them must be present in the medical record.

- **Bleomycin-induced pneumonitis (NIB):** Bleomycin is an antibiotic with antitumor effect discovered in 1966, originally isolated from a fungus (*Streptomyces verticillus*). This agent is very useful for various types of tumors such as lymphomas, germ tumors, squamous cell carcinomas, Kaposi's sarcoma, cervical cancer, and head and neck tumors. The most important toxic effect of this drug is NIB. The central event for the development of this disease is endothelial damage to the pulmonary vasculature secondary to the release of cytokines and free radicals that can result in pulmonary fibrosis. It can manifest itself clinically gradually during treatment and up to 6 months after it has been discontinued. The clinical manifestations are very similar to those of infectious pulmonary pictures, so the final diagnosis of NIB is by exclusion.

Other diseases are excluded through negative sputum cultures, PCR for viruses, or serological determinations for specific lung pathogens. Generally, these patients are medicated with antibiotics but they evolve in a torpid way.

Other studies that help the diagnosis of pulmonary fibrosis are those that evaluate lung volumes. Although there are no proven effective treatments, corticosteroids are widely used. Patients who survive NIB fully recover lung capacity and normalize the chest radiograph.

- **Mucositis:** even though approximately 75% of cancer patients develop mucositis of variable degrees after chemotherapy, only 40% of the total have solid tumors. Of this group, the most affected are those patients with head and neck tumors who receive combined treatment with chemotherapy and radiotherapy. Mucosal damage is an important factor in the development of systemic infections in previously colonized patients. Some microorganisms exacerbate the lesions and consequently increase the susceptibility to systemic infections by other commensal microorganisms. The clinical presentation of infectious mucositis can be indistinguishable from those induced by drugs. It is characterized by the presence of erythema, ulcers, bleeding, or exudate.

The list of drugs that cause mucositis is extensive, but among the most common are: methotrexate, 5-fluorouracil, cisplatin, cytarabine, and etoposide. The course of the disease after a standard or high dose of chemotherapy drugs parallels the neutropenia that occurs in these patients. The first manifestations are seen near the nadir of neutropenia and resolve simultaneously with hematologic recovery.

Several germs are associated with systemic infections secondary to mucositis. Among the most important is *Streptococcus viridans*.

Others but less frequent are vancomycin-resistant enterococci in previously colonized anaerobic patients and there are some reports of secondary invasive fungal infections by *Candida* and *Aspergillus* sp.

Effect of corticosteroids

Corticosteroids are used in some cases as part of chemotherapy treatment and in other cases as part of supportive treatment, for example in patients with tumor lesions in the spine, or masses in the central nervous system, to reduce secondary edema. These high-dose drugs restrict the accumulation of neutrophils at the site of inflammation by reducing their adherence capacity and decreasing their chemotactic activity. They also decrease the phagocytosis of microorganisms and their intracellular death.

The loss of neutrophil function deprives the host of a primary defense mechanism against invading microorganisms, allowing infections to occur and their subsequent spread. The microorganisms most frequently associated with cellular immunosuppression generated by corticosteroids are shown in Table 1.

Table 1: Common microorganisms related to the type of immunosuppression

TYPE OF IMMUNOSUPPRESSION PATHOGENS

Impaired cell-mediated immunity. • Herpes simplex

- Herpes zoster

- Cytomegalovirus and Epstein-Bar

- Adenovirus

- Respiratory syncytial virus, Influenza and Parainfluenza

- Listeria monocytogenes

- Nocardia species

- Human papillomavirus

- Mycobacterium tuberculosis

- Nontuberculous mycobacteria

- Pneumocystis carinii

- Aspergillus species

- Cryptococcus neoformans

- Histoplasma capsulatum

- *Coccidioides immitis*
- *Toxoplasma gondii*

Frequent infections in patients with solid tumors

The population of cancer patients has increased its survival in recent years thanks to the evolution of chemotherapy treatments, being more exposed to infections.

To this are added other risk factors such as the presence of devices, nutritional deterioration, immunological alteration secondary to treatment or associated with the primary tumor, etc.

All of this alters the epidemiology of infections.

Tumors that spread into the surrounding tissues destroying the mucous and epithelial barriers produce local inflammation and subsequent necrosis, leaving in their wake a predisposed terrain for bacterial proliferation. The same happens with the obstruction of ducts such as the bronchioles, the ureters, the gastrointestinal tract, the biliary tree and the secretion ducts of the exocrine glands, which results in an accumulation of fluids favoring the development of infections.

1. Pneumonia

Patients with solid tumors have an increased risk of suffering from pneumonia but also have a higher risk of developing torpidly despite treatment.

This is attributable to various causes. The existence of an occupying lung mass in cases of lung tumors favors post obstructive pneumonia. This is characterized by infection of the lung parenchyma distal to a tumor lesion that produces bronchial obstruction. These pneumonia are generally polymicrobial and the most frequently isolated germs are the anaerobes, *S.pneumoniae*, *H.influenzae* and *S.aureus*.

The development of esophago-tracheal fistulas in cases of esophageal tumors favors the aspiration of gastric contents, producing in the first instance a chemical pneumonitis that later evolves into aspiration pneumonia. This is also common in patients with central nervous system neoplasms that present with altered consciousness, increasing the risk of aspiration. The germs isolated in these cases vary according to whether the aspiration occurs outside the hospital (*Pneumococcus*, *Staphylococcus aureus*, *H. influenza* and *Enterobacteria*) or hospital (other gram-negative bacilli including *Pseudomonas aeruginosa*). The distortion of the architecture of the upper airway in head and neck tumors and the need for a tracheostomy in patients with obstruction of the same favors the development of pneumonia caused by germs that initially behave as colonizers, predominant in these cases gram-negative bacilli.

The treatment of these patients should consider the acquisition of the disease (intra-hospital or extra-hospital), whether the patients are tracheostomized or not, and a history of possible aspiration. In this

case, the antibiotic coverage against anaerobic germs must be extended. The duration of treatment varies, depending on the clinical evolution and the isolated microorganisms, between 7-14 days. Patients with parapneumonic pleural effusion (empyema) must undergo surgical drainage and the treatment time is 21 days. It should be taken into account that in patients with poor evolution and history of aspiration, the possibility of abscess should be considered.

In this case, the treatment time should be extended and the need for combined surgical treatment should be evaluated.

2. Urinary infection

Urinary tract infections in these patients are favored, on the one hand, by the anatomical effect of the tumors, and on the other hand, by the presence of bladder devices that can be used to unblock the urinary tree or in cases of incontinence.

A single catheterization in an outpatient has a risk of infection of 1% versus 10% in an inpatient. This risk increases in patients with other predisposing factors such as cancer patients, especially of the urinary tract. The catheter colonizes with the patient's colonic flora within approximately 48-72 hours, and over time an inflammatory response is stimulated that can result in acute cystitis. It is important to bear in mind that for taking a urine culture sample in permanently catheterized patients, the urinary catheter must be replaced to avoid contamination with colonizing germs. The most frequently isolated microorganisms are the gram-negative Enterobacteria type. What varies according to each case are the resistance patterns depending on the previous use of antibiotics, whether the infection is intra-hospital or extra-hospital, etc. Based on the above, an antibiotic will be chosen that preferably covers gram-negative microorganisms (quinolones) and if the patient is hospitalized, the spectrum should be expanded according to the epidemiology in each hospital (quinolones, 3rd generation cephalosporins, carbapenems, etc.). A urinary infection in these patients should always be interpreted as complicated, so the duration of treatment should not be less than 7-10 days.

Prophylactic antibiotic treatment in patients with recurrent urinary tract infections is not recommended as it generates antibiotic resistance due to selection pressure of the colonizing flora.

3. Mucositis

The presence of mucositis is a factor that predisposes the appearance of systemic infections, mainly bacterial ones. Streptococcus viridans is responsible for up to 39% of bacteremia in neutropenic patients and several authors propose oral lesions as the gateway. Patients with ulcerative mucositis have a three times greater risk of developing systemic Streptococcus pyogenes infections than other patients. Mucositis has also been implicated as a possible contributing factor to invasive vancomycin-resistant

enterococcal infection. Invasive fungal infections represent a major problem in cancer patients but are more common in oncohematologic patients.

But in these patients, it must also be taken into account that there are infections of the mucous membranes that contribute to the subsequent development of mucositis.

For example, the frequency of reactivation of Herpes simplex type 1 in patients with head and neck tumors after combined radiotherapy and chemotherapy treatment is 15% -20%, resulting in the most frequent symptomatic viral disease. Another infection rarely described in patients with solid tumors is CMV mucositis.

4. Bacteraemia

The frequency of bacteraemia in cancer patients is related to the underlying pathology and also to the clinical condition of the patient.

The presence of microorganisms in the blood of cancer patients may reflect alterations in local conditions at the site of the neoplasm. In these cases, the tumors spread to neighboring tissues causing rupture of mucosal barriers and epithelial surfaces. This helps local inflammation and necrosis, creating a favorable environment for bacterial proliferation, especially of the endogenous flora.

In addition to the local component, there are also host factors that contribute to the development of bacteremia. For example alterations in immunity, malnutrition, tumor type and general condition.

Other important factors are the previous use of antibiotics, the type of chemotherapy and the presence of devices (urinary catheter, central venous catheter, etc.). The use of intravascular devices allows colonizing microorganisms to enter deep tissues and the bloodstream.

Bacteremia in patients with solid tumors are generally intranosocomial and in a large percentage, the entry gate (secondary bacteremia) can be identified. There are numerous publications in which the majority of bacteremia occurred in non-neutropenic patients and the associated risk factors are, firstly, a very poor clinical condition attributed to already disseminated tumors, and secondly, a history of significant weight loss.

The germs that are usually isolated vary according to the different series. The development of *Streptococcus bovis* and other streptococci in blood cultures should raise suspicion for the presence of a neoplasm of the gastrointestinal tract.

Coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Candida albicans*, and *Candida non-albicans* are also frequently isolated.

Empirical treatment should be based on physical examination, on finding the primary focus of ongoing bacteremia, and on intra- or extra-hospital origin.

Antibiotics will be adapted according to the type of microorganism and the antibiogram.

Prevention and prophylaxis measures

General measures are aimed at preventing the appearance of infections in the patient with a solid tumor and at preventing their spread. But they also aim to improve the quality of life of the patient.

→ Proper handwashing: it is the most important and effective measure to prevent the transmission of infections. It should be done preferably with antiseptic soap or alcohol-gel, before and after making contact with the patient regardless of the use of gloves.

→ Antisepsis to reduce skin-mucosa colonization: daily baths, oral cleaning with antiseptic solutions (chlorhexidine swish), or gentle brushing

→ Proper handling of catheters: use sterile gloves and a chemise for handling

→ Avoid as far as possible the use of devices in patients who do not have an absolute indication (prolonged urinary catheterization, etc.).

→ Topical treatment in patients with skin lesions with 0.25% sodium hypochlorite, is one of the best alternatives to reduce necrotic tissue. In case of developing allergy or local irritation, 4% chlorhexidine gluconate or 1% aqueous solution can be used.

→ Systemic treatment with metronidazole is also effective in reducing the number of colonies of microorganisms in necrotic tissue and consequently reduces the foul odor of this type of lesion.

→ Prophylaxis of Pneumocystis carinii pneumonia (PCP)

PCP is one of the most important opportunistic infections in the oncological population, but with a wide predominance in oncohematological patients and bone marrow transplants. Patients with solid tumors treated with high-dose corticosteroids have a 1.3% incidence of suffering from PCP, therefore prophylactic treatment is not recommended.

But this causative agent of pneumonia should be taken into account when receiving a patient of these characteristics with a compatible clinical picture.

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