

Emergencies in Oncology

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Abstract

Oncological emergencies are defined as any acute possible morbid or life-threatening events in patients with cancer either because of the malignancy or because of their treatment. With advances in antitumor therapy, the prognosis of oncological diseases has improved, so the management of their complications, whether due to the tumors themselves or their respective treatments, becomes more important day by day. These events may occur at any time during malignancy, from symptoms present to end-stage disease. Metabolic syndromes include Tumor Lysis Syndrome and Hypercalcemia. Compression Syndromes includes Superior Vena Cava Syndrome and Spinal Cord Compression Syndrome

Keywords: Oncology; Tumor lysis syndrome; Hypercalcemia; Superior vena cava syndrome; Spinal cord compression syndrome.

Introduction

Cancer is a pathology that, due to its characteristics, produces different organic phenomena capable of producing the deterioration of the individual until reaching his death if the instituted therapeutics do not achieve a resolution of it. With advances in antitumor therapy, the prognosis of oncological diseases has improved, so the management of their complications, whether due to the tumors themselves or their respective treatments, becomes more important day by day. We will develop those situations in which cancer causes rapidly evolving clinical pictures, its early recognition and treatment are essential, to avoid irreversible damage

on the one hand, and on the other, to face a rapid and precise treatment, and thus improve the quality of life. and patient survival. These situations must be quickly recognized by the treating physicians, whether they are specialists in oncology or general practitioners who attend the patient's care, that is, the existence of an oncological emergency must be considered given their presence. Now the question is, should this emergency be handled exclusively by the oncologist? The answer is no, given that patients rarely go to a specialized oncology center in the first instance, but instead go to a general hospital and there they are received by non-oncologists, hence the importance of

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knowing how to diagnose and treat these conditions [1].

Metabolic syndromes

Tumor lysis syndrome

Tumor Lysis Syndrome is known as a serious complication of the treatment of oncological diseases, developing mainly in hematological neoplasms such as Burkitt-type lymphomas and acute lymphoblastic leukemias, as well as in some solid tumors such as breast cancer, lung, metastatic breast cancer, ovary, and sarcomas. This syndrome generally occurs after chemotherapy treatment, although on some occasions it can occur spontaneously without any treatment. It basically consists of a metabolic alteration with serious electrolyte modifications that produce lactic acidosis with acute renal failure [2-4]. Oncological treatment in patients with large cell masses causes their destruction, leaving high contents of nucleic acids, potassium, phosphates, and calcium to circulate. The release of uric acid, because of the destruction of nucleic acids, tends to precipitate in the renal tubules, facilitated by the lactic acidosis produced by this syndrome. The massive release of phosphates brings about an alteration in the calcium-phosphorus metabolism that results in hyperphosphatemia with hypocalcemia with precipitation of calcium in the kidneys, leading to renal failure. It can cause hyperkalemia due to the release of potassium by the cells destroyed by the ionic imbalance produced.

Clinical presentation

The clinical picture of the patient is fundamentally based on the electrolyte alterations produced, which gives us the different complications of the picture:

- Hyperuricemia: asthenia, anorexia, hiccups, irritability, difficulties in concentration, itching, vomiting
- Hyperkalemia: paresthesia's, muscle weakness, muscle cramps, vomiting, intestinal colic, cardiac arrhythmia.
- Hyperphosphatemia: acute renal failure and hyperkalemia.
- Hypocalcemia: paresthesia's, tetany, muscle spasms, cardiac arrhythmia, seizures.

Diagnostic studies

To properly request complementary studies, an adequate questioning of the patient is essential to find out about their pathology and the previous existence of oncological treatment.

- Clinical analysis: complete blood count, ionic study, uremia, creatininemia, calcinemia and phosphoremia.
- Arterial Gas Study
- Urinary study with ionic profile
- Electrocardiogram

Treatment

Hydration: Fluids should be administered at a rate of 3000 c/c/day, an amount that can be increased if adequate urinary output is not achieved. In patients with cardiac disorders or severe anemia, hydration restricted to 1,500-1,800 cc/day will begin, transfusions will be made if necessary, and hydration will be increased after that. Monitor urinary output every 8 hours, if after the first eight hours an optimal urinary output has not been achieved, hydration should be increased by 20%. If a diuresis of 90cc/hour is not achieved [2,5-7]. Mannitol should be added a 300 to 400mg/kg (21 to 28g for a 70kg patient) or up to 100g of 15% to 20% solution IV once. Treatment should

not be repeated in patients with persistent oliguria.

Furosemide: 20 to 40mg IV or IM, increasing by 20mg every 2 hours as needed to attain clinical response. Administer IV doses slowly. A maximum infusion rate of 4mg/minute has been recommended when administering doses greater than 120mg or for patients with cardiac or renal failure. Heart failure guidelines recommend adding a loop diuretic to standard therapy for reduced ejection fraction heart failure (HFrEF) patients with volume overload. Diuretics should also be used in preserved ejection fraction heart failure (HFpEF).

Hyperuricemia: Allopurinol should be administered at a dose of 900mg/day divided into three doses. Urine pH should be maintained within a range of 6.5-7.5 with the use of Sodium Bicarbonate at a dose of 120mEq/day (strictly control the pH since an excess in the administration of bicarbonate can produce alkalosis and cause sodium phosphate precipitation). calcium instead of uric acid).

Hyperkalemia: Administration of 10% Calcium Gluconate at a dose of 100-200mg/Kg/dose slowly intravenously with electrocardiographic control.

Hyperphosphatemia: Oral aluminum hydroxide will be indicated at a dose of 150mg/kg/day divided into three doses [8,9].

Hypocalcemia: Calcium gluconate 100mg/kg/dose will be administered every 6-8 hours, monitoring heart rate.

Indications for dialysis include persistent hyperkalemia or hyperphosphatemia despite treatment, volume overload, uremia, symptomatic hypocalcemia, and hyperuricemia. Hemodialysis is preferred

over peritoneal dialysis because of better phosphate and uric acid clearance rates. Continuous hemofiltration also has been used and is effective in correcting electrolyte abnormalities and fluid overload. Because hyperkalemia can recur after dialysis is initiated and because of the high phosphate burden in some patients with tumor lysis syndrome, electrolyte levels must be monitored frequently and dialysis.

Hypercalcemia

Generalities

Hypercalcemia is the most common metabolic complication in cancer patients. It has been reported in up to 20-30% of patients, in some of the stages of the disease. This incidence may be in decline associated with the widespread use of bisphosphonates in patients with multiple myeloma or breast neoplasms, despite the lack of data to certify this statement [9,10]. Hypercalcemia in cancer patients contributes significantly to morbidity and mortality and can present diagnostic difficulties and dilemmas in relation to its therapeutic management. Of all the causes of hypercalcemia, that associated with tumors is the most frequent in hospitalized patients. The most important causes of hypercalcemia are:

1. Primary hyperparathyroidism 54%
2. Tumors 26% (Lung 35%, Mom 25%, Hematological T. (myeloma, lymphoma) 14%, Head and neck T. (squamous cell carcinoma) 8%, Kidney 3%, Prostate 3%, Primary tumor of unknown origin 4%, Other tumors 8%)
3. Other causes 20% (Hypervitaminosis D and A, Immobilization, Osteoporosis,

Paget's disease, Hyperthyroidism, Pheochromocytoma, Addison's disease, HIV, Tuberculosis, Sarcoidosis, Milk-alkali syndrome, Lithium, Thiazides, Chronic renal insufficiency, Familial hypercalcemia hypocalciuric)

The frequency with which each tumor develops hypercalcemia is approximately: lung 27%, breast 25%, myeloma 7%, head and neck 7%, unknown primary <5%, lymphoma/leukemia, or gastrointestinal tumors 4%. Diagnosis of hypercalcemia high degree of suspicion is necessary, since some symptoms are nonspecific and attributable to other causes such as drowsiness, constipation, etc. The most frequent clinical manifestations of hypercalcemia affect the digestive system, kidneys, osteomyoarticular system, and cardiovascular system.

In severe cases, there is progressive mental deterioration, reaching coma, and kidney failure. The appearance of hypercalcemia in oncological patients has a poor prognosis, since approximately 50% of them die within 30 days after the event. It is important to

remember the differential diagnosis of tumor-associated hypercalcemia versus hypercalcemia due to primary hyperparathyroidism. In the latter case PTH is elevated, while in the former the blood level of PTH is normal or low [11,12].

Pathophysiology

Calcium metabolism is fundamentally regulated by:

1. Parathormone (PTH): Increases renal tubular and bone reabsorption of calcium. It is an osteolytic protein, and hypercalcemic.
2. Calcitonin: decreases calcium reabsorption both at the bone and renal tubular levels; therefore, it produces an increase in calciuria.
3. Active metabolites of vitamin D (or calciferol): 1.25 di OH cholecalciferol or vitamin D₃ or calcitriol: all of them promote tubular and intestinal reabsorption of calcium.

Classification

Hypercalcemia in cancer patients can be classified into four subtypes (Table 1):

PTH Phosphate Level Metastasis	Mechanism of hypercalcemia Frequency
Type 1	Local Osteolysis Normal Decreased Large Amount Local release of cytokines 70-80%
Type 2	HHT Diminished Independ. Protein in blood with active PTH 20-30%
Type 3	Hypercalcemia due to vitamin D ₃ secretion
Type 4	Hypercalcemia due to increased PTH secretion Increased bone reabsorption and Ca retention by kidney <1%

Table 1: Classification of Hypercalcemia.

Type 1: Patients with osteolysis and hypercalcemia

Exists in this form, the second most frequent tumor hypercalcemia (about 20%),

high number of bone metastases. Hypercalcemia occurs as a result of osteoclastic resorption around malignant cells; This is the result of the local production of cytokines (tumor necrosis

factor, interleukin 1 and 2, prostaglandins, etc). It presents with normal levels of phosphatemia and low PTH.

Type 2: Tumor humoral hypercalcemia (HHT)

Product of the secretion of a protein with parathyroid hormone function (PTHrP: parathormone related protein), by the tumor. This type of hypercalcemia occurs in 80% of cases of tumor-associated hypercalcemia. PTHrP was identified in the 1980s as a product of tumor secretion; with the ability to activate PTH receptors and produce hypercalcemia [15]. Like PTH, PTHrH increases bone resorption and calcium retention in the kidney. It also induces local osteolysis around bone metastases; It also seems to be related to the progression of bone metastases in patients with breast cancer. Although the tumors most frequently associated with HHT are squamous cell tumors (of the head and neck, esophagus, cervix, or lung), kidney, ovarian, endometrial, and breast cancer, and HTLV-associated lymphoma, any tumor can produce this protein. PTHrH has also been found in non-tumor tissues, so it is interpreted that this protein would have different functions in normal tissues, both fetal and adult (epithelia, mesenchymal tissues, glands, hair follicles, placenta, etc.), which are still being studied. they are investigating. Just as an example, and from what was learned in experimental models in rodents, it was seen that PTHrH is related to the development of teeth, with breast development, lactation, it is concentrated 1000 times the serum value in breast milk, and is related to the intestinal development of infants, it is also associated with the correct development of cartilage. Other tissues that have a high concentration of

PTHrH are the epithelial tissues and the nervous system [13,14].

Type 3: Hypercalcemia due to Vitamin D secretion

Hypercalcemia, in this case, occurs because of the secretion of 1, 25 OH vitamin D by the tumor. This active metabolite of vitamin D produces an increase in osteoclastic activity on the one hand, and on the other, an increase in the intestinal absorption of calcium. This type of hypercalcemia is associated with all types of lymphomas. Statistically, it is a rare cause of tumor-associated hypercalcemia (<1% of cases).

Type 4: Hypercalcemia due to PTH secretion

There is ectopic secretion of parathyroid hormone (PTH). This cause is highly uncommon (<1% cases).

Clinic manifestation

In general, if the calcinemia is less than 13 mg/dl, there are no clinical symptoms. Initial symptoms are nonspecific and include anorexia, constipation, nausea, vomiting, polydipsia, and polyuria. In the long term, nephrolithiasis and chronic renal failure may develop.

Symptoms of hypercalcemia

General Signs: Dehydration, weight loss, pruritus, asthenia, Gastrointestinal Anorexia, constipation, nausea, vomiting, abdominal pain, Skeletal muscle Weakness, bone pain, ataxia and tiredness, Genitourinary Polydipsia, polyuria, nephrolithiasis, renal failure, Nervous System Hyporeflexia, seizures, headache, confusion, drowsiness, lethargy, coma, Cardiovascular Bradycardia, heart blocks, arrhythmias, asystole, PR lengthening, QT

shortening, QRS widening, ST abnormalities, increased sensitivity to digitalis [15,16].

Diagnosis

In general, when calcinemia is measured, the total calcium in the blood is measured; ionic (or active) calcium accounts for 45% of serum calcium, the rest is protein bound. Therefore, variations in the albumin level can produce significant changes in the actual calcium. Thus, in any case where the protein level is in question, it is useful to measure ionized calcium. There are, on the other hand, certain myelomas in which proteins with the ability to bind to serum calcium are produced; in these cases, calcinemia would overestimate the level of ionized calcium. In alkalosis, on the other hand, protein binding is increased. Therefore, the Corrected Calcium: $\text{total Ca}^+ (0.8/\text{dl for every } 1\text{g/dl of albumin } < 3.5)$. Since this equation is not always reliable, the dosage of ionic calcium is recommended, whenever there is doubt about the validity of the calcinemia data [17].

Diagnostic guidelines

Consider causes related to the underlying disease: In general, tumors associated with hypercalcemia are large, and by the time hypercalcemia is found, the oncological diagnosis is already made; except for small neuroendocrine tumors, whose diagnosis is often made as a consequence of the appearance of hypercalcemia, which leads to studying the patient. Look for causes that are independent of the underlying disease: For example: primary hyperparathyroidism, use of thiazides, granulomatous diseases. Studies that should be ordered when evaluating a cancer patient with hypercalcemia:

1. PTH dosage: Although ectopic secretion of PTH as a cause of hypercalcemia is highly uncommon (see classification subtypes), tumor-associated primary hyperparathyroidism is not.
2. Dosage of phosphoremia and creatininemia: Hypophosphatemia can lead in experimental models to hypercalcemia. Hypercalcemia, on the other hand, affects the renal mechanisms associated with the excretion of sodium and calcium, which is why, in severe cases of hypercalcemia, renal failure is the rule. PTH and PTHrH also act on the renal tubules, increasing calcium reabsorption.
3. Dosage of total proteins and albumin
4. PTHrP dosage: Whenever tumor humoral hypercalcemia (HHT) is considered.
5. Dosing 1, 25 OH vitamin D in blood: If sarcoidosis or other granulomatous diseases or lymphomas are suspected.
6. ECG
7. Arterial blood gases
8. Bone scan: To assess the bone mass affected by tumor.

The serum calcium level may be mildly, moderately, or severely increased

Types of Hypercalcemia: Mild hypercalcemia (10.5mg/dl, 2.6mMol/l 11.9mg/dl, 2.9mMol/l) (Table 2)

Hypercalcemia, moderate (12mg/dl, 3mMol/l 13.9mg/dl, 3.4mMol/l, > 14mg/dl, >3.5mMol/l)

The appearance of symptoms (fundamentally neurological and renal) in hypercalcemia is related to three factors:

Type	Frequency	Bone Metastasis	Causal Agent	Typical Tumors
Local Osteolytic Hypercalcemia	20%	common/ extensive	Cytokines, chemokines, PTHrP	Breast Cancer, Lymphoma, Multiple myeloma
Humoral Hypercalcemia of Malignancy	80%	Minimal/absent	PTHrP	Squamous cell cancer (e.g., lung, head and neck, esophagus, or cervix), renal cancer, breast cancer, endometrial cancer, ovarian cancer, HTLV-associated lymphoma
Hypercalcemia from 1,25 (OH) ₂ D-secreting lymphomas	<1%	Variable	1,25 (OH) ₂ D	Lymphoma (all forms)
Hypercalcemia from ectopic hyperparathyroidism	<1%	Variable	PTH	Variable

Table 2: Types of Hypercalcemia that are associated with Cancer.

1. The degree of hypercalcemia.
2. The rate of rise in serum calcium: the faster the calcinemia rises, the more important the symptoms will be, and the faster their appearance.
3. Pre-existing neurological or renal pathology: in the elderly, for example, with some degree of cognitive impairment, moderate hypercalcemia may be more symptomatic than in young people. The elderly, due to the physiological changes associated with aging processes, tend to tolerate hypercalcemia or any other metabolic alteration less well. In some cases, they also require a somewhat different therapeutic management than younger patients.
4. Concomitant administration of sedatives or narcotics: on the one hand, this type of medication can mask certain symptoms, thus delaying diagnosis; and on the other

it can aggravate the neurological symptoms of hypercalcemia [18,19].

Therapeutic considerations

There are two possible scenarios in relation to an episode of hypercalcemia. The first case is that of a tumor already diagnosed, controlled, under treatment. The management of hypercalcemia should be understood only as the management of a complication of the underlying pathology. What is achieved with the treatment is to "buy time", so that it can take lie down for chemotherapy, radiation therapy, or any other antineoplastic treatment to take effect. The second scenario is one in which there is no possible control of the underlying disease, and therefore, the management of hypercalcemia is part of the support treatment and must be considered in each case. The treatment decision will be made based on the levels of hypercalcemia (see Table 3). In mild asymptomatic hypercalcemia, good hydration and salt supplements are generally sufficient. In

more severe cases of hypercalcemia, the treatment will be carried out with:

1. Hydration with saline solution and Calciuresis: Patients with tumor-associated hypercalcemia are usually dehydrated due to renal difficulty in concentrating urine (nephrogenic diabetes insipidus). Dehydration can lead to significant volume depletion, up to 5 to 10 liters. Therefore, the initial measure should consist of volume expansion, to correct dehydration, increase glomerular filtration rate, and promote renal calcium excretion (calcium and sodium excretion are parallel in the renal tubules). In addition, saline has an effect on the proximal convoluted tubule by inhibiting calcium reabsorption. In mild cases, hydration can be orally, in moderate or severe cases the intravenous route should be used. Use physiological solution 300 to 500ml/hour for the first 3 hours, and then 500 every 3 hours up to a total of 3 to 5l in 24 hours. Control during hydration hourly diuresis, PVC, cardiovascular and renal functions. Calcemia reduction should be around 0.5 to 2mg/dl. Once the patient is rehydrated, a forced diuresis with furosemide can be given, if necessary. The dose of intravenous furosemide is 20 to 40mg every 6 to 12hours. The response must be monitored, in each case to prevent sodium loss from leading to a paradoxical situation of decreased renal excretion of both sodium and calcium. Potassium and magnesium should be monitored and eventually replenished if necessary [20]. In case

of kidney failure, treatment should be with dialysis.

2. General measures include:
 - a) Withdraw calcium supplements from enteral or parenteral feeding.
 - b) Avoid immobility
 - c) Withdraw medications that can themselves cause hypercalcemia (thiazides, lithium, calcitriol, vitamin D).
 - d) If it is possible to minimize the use of sedatives, analgesics, etc. to improve the neurological status of the patient.
 - e) Control phosphatemia. In general, patients with hypercalcemia have hypophosphatemia, which in turn increases the level of calcium in the blood (seen experimentally in animal models). Hypophosphatemia is associated with the use of loop diuretics, decreased dietary phosphorus intake, treatment with calcitonin, or antacids.
 - f) Administer neutral phosphate orally or by nasogastric tube, so as to maintain phosphate levels between 2.5 and 3mg/dl (0.98 to 1mMol/l); and the calcium/phosphorus product less than 40 (ideally close to 30). Only in extreme cases use the intravenous route, since it can cause severe hypocalcemia, seizures and acute renal failure.
3. Antiresorptive measures: Although these treatments are slower than rehydration and forced diuresis, they are also more durable. Its objective is to decrease bone resorption.
4. Calcitonin: It inhibits bone resorption, increases calciuresis, and has a mild analgesic effect. It is

an important drug because its action is fast (from 2 to 4 hours, with a peak of action at 24 to 48 hours), but short (lasting 2 to 4 days), due to the development of tachyphylaxis. It is not necessary to correct the dose in dehydration or renal insufficiency. Dose: 4 to 8IU/Kg every 6 to 12 hours, subcutaneously or intravenously. Maximum use 8 days. It reduces calcium by around 0.5 to 3mg/dl [21-23].

5. Corticosteroids: Very useful in hypercalcemia associated with granulomatous diseases, and neoplasms sensitive to corticosteroids such as myelomas, lymphomas, and leukemias. Sometimes also in mom. It should not be used on other tumors. Its mechanism of action is to decrease the levels of 1 – 25 oh vitamin D₃. Dose: 100 to 400mg per day of prednisone (or equivalent). Its effect is expressed a week, lasts 3 to 4 days, and manages to reduce calcium levels by 0.5 to 3mg/dl.
6. Bisphosphonates: They inhibit calcium reabsorption by osteoclasts by binding to the hydroxyapatite surface. They are the most important therapeutic novelty provided in recent years, safe and effective in the long term in the treatment of bone metastases in many solid tumors, and in multiple myeloma. They manage to normalize calcium in 70% of patients, can have an analgesic effect on bone metastases, and prevent vertebral fractures in some tumors, such as myeloma. In fact, the possibility of standard treatment with bisphosphonates in tumors

such as breast, prostate, etc. is raised in the literature. Treatment with bisphosphonates should be started as soon as hypercalcemia is diagnosed, since the onset of its action takes about 2 days. Pamidronate is the most widely used of the bisphosphonates., in doses of 60 to 90mg intravenously to pass in 2 to 4hours. It must be started between 24 and 72hours, and its effect lasts 3 to 4weeks. It can produce side effects such as gastrointestinal symptoms, fever, local reaction, hypokalemia, hypomagnesemia, and hypophosphatemia. (Table 4). Other more recently introduced bisphosphonates seem attractive due to the possibility of also being administered orally, such as ibandronate, or clodronate, which can be administered as a subcutaneous infusion. Zoledronate has the advantage of its simple form of administration, in rapid infusion (4mg infusion of about 15 minutes). Both pamidronate and zoledronate can cause kidney failure after being administered in vs doses. The dose should be corrected when creatinine is >3mg/dl. In case of poor response, or less response than expected, a second dose of bisphosphonate can be added, or combined with another hypocalcemic drug [24,25].

7. Mithramycin or plicamycin: Inhibitor of RNA synthesis in osteoclasts. The onset of its action is between 12 and 72hours, but its duration is unpredictable (between 2 and 14 days). Due to this and its important toxicity (hepatotoxicity, and nephrotoxicity in addition to

producing bone marrow suppression in the 3 series, nausea, and vomiting), its use is very limited. It is administered intravenously, in a central line, at a rate of 25mg/kg in infusion over 4 to 6hours. It can be repeated at 24 to 48hours.

8. Gallium nitrate: Potent inhibitor of bone resorption. It requires a complex administration mechanism: 200mg/m² of body surface per day in a continuous infusion for 5 days. May cause adverse effects such as nausea, vomiting, hypophosphatemia, and nephrotoxicity.
9. Other treatments: Oral phosphate, for chronic treatments, hemodialysis in patients with hypercalcemia and kidney failure, prostaglandin synthesis inhibitors, etc. Experimentally, in animal models, anti-PTHrH monoclonal antibodies are being worked on.

Forecast

50% of cancer patients with hypercalcemia die in the following month, and 75% in the 3 months after the episode. The prognosis is somewhat better in those patients who respond to specific antineoplastic

treatment. However, it must be remembered that the treatment of hypercalcemia does improve the symptoms, and therefore the patient's quality of life [26].

Compression syndromes

Introduction

Superior vena cava syndrome is a medical and oncological emergency. The cause of its origin is usually a malignant tumor located in the chest. It is the manifestation of the obstruction of the superior vena cava. This syndrome is a series of symptoms that can appear in patients with lung cancer, non-Hodgkin lymphoma and other types of cancer and for causes not related to cancer. This condition is serious for adults and can lead to death in children. Basically, this syndrome is caused by impaired blood flow through the superior vena cava to the right atrium [26,27]. The first description of this syndrome was in a patient with a syphilitic aneurysm in 1757 by William Hunter. In 1954 Schechter reviewed the well-documented cases of this syndrome, observing that 40% of them were due to syphilitic aneurysms or tuberculous mediastinitis. Currently, these entities have almost disappeared, with small cell lung cancer being the origin of this syndrome in approximately 80% of cases. (Figure 1,2).



Figure 1: Patient with Superior vena cava syndrome.



Figure 1: Patient with Superior vena cava syndrome.

Pathophysiology

Knowledge of the anatomy of the superior vena cava and its relationship with the surrounding lymph nodes is essential for understanding the development of this syndrome. The superior vena cava is formed by the confluence of the right and left brachiocephalic veins in the middle third of the mediastinum. The superior vena cava extends caudally for 6 to 8cms, terminating in the right atrium, extending anteriorly into the right main bronchus. The azygos vein joins the superior vena cava posteriorly by bending into the right main bronchus and is posterior to and to the right of the descending aorta. The parietal mediastinal pleura is lateral to the superior vena cava, creating a limited space, and the superior vena cava is adjacent to the right peritracheal, azygous, right hilar, and subcarinal lymph node groups. The vessel is thin-walled, and the blood flowing through it is under low pressure.

Thus, when the lymph nodes or the ascending aorta increase in size, the superior vena cava is compressed, the blood flow slows down and can even cause total occlusion [28,29]. The severity of the syndrome depends on how quickly the obstruction began and its location. The earlier the onset, the more severe the

symptoms and signs because the collateral veins do not have time to distend to accommodate increased blood flow. If the obstruction is above the entrance of the azygos vein, the syndrome is less pronounced because the azygos venous system can easily distend to accommodate diverted blood so there will be less venous pressure affecting the head, arms, and chest. superior. If the obstruction is below the entrance of the azygos vein, more marked symptoms and signs are observed because the blood has to return to the heart through the superior abdominal veins and the inferior vena cava, which requires a higher venous pressure.

Epidemiology and etiology

Epidemiology

As mentioned, the superior vena cava syndrome is the external obstruction to the blood flow of the superior vena cava due to neoplastic diseases (observed in 7% of cancer patients) or non-neoplastic diseases such as fibrosis due to inflammatory conditions or thrombosis. Until 1950, approximately 70% of the cases of this pathology corresponded to infectious diseases (mainly syphilis) and the rest to neoplastic pathologies. In a review of cases carried out around the 1980s, 90% of the

cases were caused by a neoplastic disease (most frequently lung cancer and lymphoma). Given the severity of this condition, survival at 24 months is 3% of patients [37,30].

Etiology

1. Neoplastic Origin
 - a) Small Cell Lung Cancer 82%
 - b) Non-Small Cell Lung Cancer Epidermoid Variety 26%
 - c) Non-Small Cell Lung Cancer Adenocarcinoma Variety 14%
 - d) Non-Small Cell Lung Cancer Large Cell Variety 8%
 - e) Non-Hodgkin lymphoma 12%
 - f) Hodgkin lymphoma 1%
 - g) Other 1%
2. Non-Neoplastic Origin
 - a) Intrathoracic goiter
 - b) Fibrosing mediastinitis due to Histoplasmosis mostly
 - c) Sarcoidosis
 - d) Catheter-Associated Thrombosis (Peritoneum-venous Shunts, Swan-Ganz, Feeding Catheters)
 - e) Pacemaker Associated Thrombosis

Clinical manifestations

Once the syndrome is recognized, prompt medical attention is important, but the diagnosis must first be established before starting treatment due to:

- 75% of patients have symptoms and signs for more than a week before seeking medical attention.
- Patients who present origin of this syndrome due to a neoplastic disease do not die from it but from the degree of tumor disease presented.

- A low percentage of patients with this syndrome is of non-neoplastic origin.

In the absence of tracheal obstruction, superior vena cava syndrome is unlikely to be life-threatening and treatment is not warranted before a definitive diagnosis.

The most frequent clinical findings are: Facial Edema 50%, Upper Extremity Edema 18%, Dyspnea 63%, Thoracic Vein Distention 66%, Jugular Vein Distention 54%, Facial Plethora 19%, Cyanosis 20%, Cough 24%, Chest pain 15%, Other Reddening of the palms of the hands and mucous membranes, headache and Decrease of the State of Alert

Diagnosis

The complementary studies to be carried out can be:

- Simple Chest X-Ray: Used for diagnosis in a high percentage of patients, signs of mass in the upper mediastinum with pleural effusion predominantly on the right side are observed
- Computed Axial Tomography: It can provide more subtle information than Simple Chest X-ray regarding the origin of the disease and more accurately reports mediastinal lymph node involvement.
- Nuclear Magnetic Resonance-Contrast Venography - Radio isotopic Venography: they can more accurately determine the anatomical site of the obstruction causing the condition.
- Thoracentesis - Sputum Cytology-Transthoracic Puncture-Mediastinoscopy

- Lymph node biopsy: they can provide an etiological diagnosis [31,32].

Treatment

The treatment of Superior Vena Cava Syndrome basically depends on the original etiology of the syndrome and the severity of the condition presented by the patient. Only emergency treatment of the patient is indicated in the presence of cerebral edema, decreased cardiac output or airway obstruction. In the absence of these symptoms, the etiology of this syndrome should first be sought.

Medical treatment

It is based on support measures such as:

- Elevation of the head of the bed- Oxygen therapy: they reduce cardiac output and improve venous pressure
- Corticoid therapy: reduce edema and improve symptomatology
- Diuretics and Decreased Salt Intake: reduce edema with symptom improvement

Radiotherapy

It is the treatment of choice in patients who present this syndrome due to neoplastic origin and specifically due to non-small cell lung cancer with a response rate of 46% and in small cell lung cancer a response rate between 62 and 80%.

There are differences between the schemes to be used given that until now no substantial difference has been found between them. One of the most widely accepted regimens is a 3-week regimen of (g) administered once weekly with a total dose of 24Gy.

Chemotherapy

Indicated in patients diagnosed with lymphoma or small cell lung cancer using the specific treatment for each pathology. Rapid initiation of chemotherapy can give response rates approaching 80%.

Thrombolysis

When the origin of the syndrome is a thrombus, thrombectomy can be performed with or without plasminogen activator or other thrombolytic agents such as streptokinase or urokinase.

Placement of Endovascular Prostheses

It is a new treatment methodology where highly qualified personnel are required for its use, not available in all medical care centers. It consists of the placement of prostheses (Stents) inside the vena cava. They give a rapid improvement of the patient's symptoms.

Surgery: It consists of the surgical Bypass of the Superior Vena Cava; it is more appropriate for patients with non-oncological etiology.

Cord compression syndrome

Introduction

Medullar Compression, because of a malignant disease, can be defined as the indentation, displacement or encasing of the thecal sac that surrounds the bone marrow and the cauda equina, by metastasis of epidural location or a locally advanced tumor that proliferates in the anterior or posterior region of the vertebral body and invades the vertebral canal [32] (Figure 3). It is the second neurological complication after the metastases of the Central Nervous System, whose presence leads to a significant deterioration in the quality of life

of the patient and her family. Spinal Cord Compression is a complex event that deserves the interaction of the multidisciplinary team early to reduce the deficit consequences from the neurological point of view. The natural history of the condition, if not treated, is governed by pain, paralysis, sensory deficit, and sphincter dysfunction [33].

Epidemiology

The evidence suggests that between 2.5-5% of patients with terminal illness present Spinal Cord Compression within the last two years of its evolution. There is a clear and strong association between the behavior of tumors to metastasize to the spine and the risk of Spinal Cord Compression. In adults with prostate, breast, and lung cancer, approximately 15-20%, for each one, will present this complication.

Pathophysiology

The main pathophysiological mechanism is given by hematogenous embolization of malignant cells, especially clonogenic cells with affinity for bone marrow through Batson's valved venous plexus. This dissemination results in a mass in the vertebral body that grows and affects the thecal sac, compressing the spinal cord and the epidural venous plexus. The earliest injury process is due to vasogenic edema of the white matter, with cytokines, inflammatory mediators and neurotransmitters playing an important role. The presence of Vascular Endothelial Growth Factor (VEGF) is associated with spinal cord hypoxia and has been implicated as a potential mechanism of damage following injury. Several observations suggest that the beneficial effect of corticosteroids would be partially mediated

by the decrease in the regulation of the expression of the Vascular Endothelial Growth Factor. Dexamethasone also decreases tissue tension and thus postpones the onset of paralysis. Bone marrow changes can vary in severity, from reversible edema to irreversible necrosis because of ischemia and infarction, depending on the degree of decreased blood flow through the perforating arteries and draining veins [34,35].

Clinical presentation

Location: According to the anatomical level, 60-80% of the compressive conditions settle in the dorsal column, 15-20% in the lumbosacral spine and less than 10% in the cervical spine. About 50% of patients are involved in more than one region.

Signs and symptoms

- **Pain:** It is present in 80-95% of patients with Spinal Cord Compression at the time of diagnosis, with an evolution of approximately 8 weeks. At the beginning the pain is localized, but its intensity increases progressively, which can be punctual or radicular. Punctual pain is present in almost all cases and is generally close to the site of injury, it is usually constant, dull, and progressive, which worsens with decubitus (due to compression of the venous plexus), movement, sneezing, effort, or flexion of the neck (Valsalva mechanism). The level involved can be established by spinal percussion. Radicular pain is located one or two levels from the compression site, is generally intermittent and discharges. Bilateral barbell pain is characteristic of thoracic spine

injuries, while unilateral pain is more common in the cervical or lumbar spine and may involve a shoulder or lower limb.

- **Motor deficit:** It is present in 60-80% of patients on admission, of which two thirds are not ambulatory, and it is the second most frequent sign. The decrease in strength increases its evidence when it affects the proximal muscles creating difficulty in walking, climbing stairs or climbing and getting up from a chair. Initial neurological status is the most important predictor of post-treatment function, which emphasizes the need for early diagnosis even before the onset of motor deficits.
- **Sensory deficit:** It is detectable in 40-90% of patients and precedes or accompanies the motor deficit. The sensory level is usually one or two segments below the compression level. It can manifest as sensory loss (hypoesthesia), paresthesia's, hiccups or areflexia. Loss of proprioception can cause ataxia, which is It occurs when there is injury to the posterior column [36].
- **Bladder and sphincter dysfunction:** These autonomic alterations tend to occur late in evolution and define the degree of neurological deterioration and are associated with a poor prognosis. Symptoms include urinary urgency, urinary retention, constipation, and impotence.

Diagnosis

The clinical suspicion of Spinal Cord Compression must be confirmed by imaging

methods, not only to define the diagnosis, but also to implement, as soon as possible, the therapeutic strategies that can lead these patients to the least possible functional deficit. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are established as the best tools for diagnosis and management of Spinal Cord Compression.

- **Conventional Radiology:** Since the introduction of CT and MRI, the role of conventional radiology has diminished, with an estimated 17% or more false negatives.
- **Bone scan:** It is not used routinely for the diagnosis of Spinal Cord Compression specifically.
- **Myelography:** The introduction of a radiopaque contrast material inside the thecal sac, allows defining the level and extent of epidural compression, and before the advent of CT, it was the fundamental pillar in the diagnosis of Spinal Cord Compression.
- **Computed Tomography (CAT):** This methodology offers the possibility of diagnosing spinal cord compression and finding paravertebral masses. Although soft tissue and bone marrow structures are better defined by MRI, CT is crucial for planning the management of spinal cord compression. disease, especially for surgery. For Radiotherapy planning, CT allows generating the dose plan if the conformed three-dimensional shape is programmed, even if MRI is used for diagnosis [37].
- **Magnetic Nuclear Resonance (MRI):** The imaging method of choice in the definition of Spinal Cord Compression is MRI because it is

non-invasive, has high resolution for soft tissues, offers images in different planes and can reconstruct them. MRI has a sensitivity of 93% and a specificity of 97%, with a diagnostic certainty of 95% in the detection of spinal cord compression. It can differentiate between benign and malignant causes of compression, with a sensitivity of 97%, specificity of 100% and an overall certainty of 98%, with imaging of the entire spine being recommended. Gadolinium-enhanced technique improves visualization of intramedullary metastases, leptomeningeal compression, and paravertebral masses.

- Positron Emission Tomography (PET): The images obtained by PET show the metabolic characteristics of the tissues from the increased uptake of 18-FDG in the metastatic sites, and as proof of functional definition of the underlying spinal cord, however the anatomical resolution of the lesions is poor compared to MRI [38,39].

Treatment

Patients diagnosed with Epidural Compression should be treated urgently to minimize possible neurological sequelae. Loss of ambulation or sphincter function prior to therapy is associated with poor response to therapy and poor prognosis. The goals of treatment are preservation or preservation of neurologic function, pain palliation, prevention of local recurrence, and preservation of spinal column stability. Although untreated spinal cord compression is not fatal, its consequences are devastating, and loss of ambulation is

associated with shorter survival. The specific therapeutic tools available for the management of this oncological emergency are corticosteroids, radiotherapy and surgery, the choice of the last two being based on the characteristics of each patient. Patients with unstable spinal column, without histological diagnosis, rapid progression of neurological deterioration, or compression of the spinal cord by bone fragments should be considered susceptible to surgery, others can be treated only with radiotherapy. Chemotherapy is an alternative in those sensitive tumors, but in a second therapeutic stage after the first moment of emergency has passed or when the patient is not a candidate for Surgery or Radiotherapy [40].

- Corticosteroids: When the diagnosis of Spinal Cord Compression is confirmed, dexamethasone should be administered, which generates a benefit that is given by the reduction of edema, inhibition of the inflammatory response, stabilization of the vascular membrane, and postpones the neurological deficit. Its use is defined but not its dosage, which can range between 16 and 100 mg per day.
- Radiotherapy: it is effective in preventing neurological damage in many patients and, in general, reduces the pain caused by spinal cord compression. The definition of the neurological status saw treatment is a predictor of evolution, which depends on the extent of functional limitation, type of tumor, and the speed of onset of neurological symptoms. Radiotherapy maintains ambulation in approximately 80-100% of

patients who started it on an outpatient basis. Approximately one third of patients with deficit but not paraplegics recover mobility, as well as 2-6% of paraplegics. The importance of tumor type in determining treatment is important since some tumors (myeloma, breast, prostate, lung) are more sensitive than others (melanoma, kidney), and the chances of functional recovery or prolonged response in these locations are lower than in radiosensitive tumors.

- Radiotherapy Techniques:
 - a) Conventional external radiotherapy: Dose schemes can vary: 30Gys in 10 fractions, 8Gys in 1 fraction, 20Gys in 5 up to 40Gys in 20 fractions. Although the optimal dose scheme has not yet been defined, the most common is 25-36Gys in 10-15 fractions.
 - b) Intensity Modulated Radiotherapy: Three-Dimensional Conformal Radiotherapy Modality.
 - c) Particle Therapy: use of Protons.
 - d) Radiosurgery: refers to the use of a single, high dose of radiation delivered under stereotaxic guidance to a well-defined tumor volume.
- Surgery: Surgery is the only method that allows immediate relief of Spinal Cord Compression and direct mechanical stabilization of the diseased and unstable spine. Indications for surgery include any

patient who can tolerate decompression and fixation, cases of direct compression by bone fragments that do not respond to radiotherapy, unstable spine where fixation and stabilization is the only way to preserve ambulation, lack of response to radiotherapy, to progressive sphincter dysfunction [41,42].

The different techniques are:

- Laminectomy: it is the removal of the posterior arch of the vertebra, decompressing the canal and the spinal cord, but it can only be implemented when the compression is posterior, since in anterior compressions there is a decrease in vertebral stability when the anterior elements are removed, leading to deterioration. Neurological [43,44].
- Anterior decompression: Allows the total removal of the pathological vertebral body and the tumor mass. The vertebra is replaced by cement and fixation artifacts [45,46].

Conclusion

Whenever possible, surgical management should be offered to the patient with Spinal Cord Compression. Radiotherapy is an excellent complement to surgery and can be used as the only treatment in non-operable patients or when palliation is the objective.

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