In spite the new informations about the physiology and biochemistry of pain, it remains true that pain is only partially understood. Cancer pain is often experienced as several different types of pain, with combined somatic and neuropathic types the most frequently. If the acute cancer pain does not subside with initial therapy, patients experience pain of more constant nature, the characteristics of which vary with the cause and the involved sites. Chronic pain related to cancer can be considered as tumor-induced pain, chemotherapy-induced pain, and radiation therapy-induced pain. Certain pain mechanisms are present in cancer patients. These include inflammation due to infection, such as local sepsis or the pain of herpes zoster, and pain due to the obstruction or occlusion of a hollow organ, such as that caused by large bowel in cancer of colon. Pain also is commonly due to destruction of tissue, such as is often seen with bony metastases. Bony metastases also produce pain because of periostal irritation, medullary pressure, and fractures. Pain may be produced by the growth of tumor in a closed area richly supplied with pain receptors (nociceptors). Examples are tumors growing within the capsule of an organ such as the pancreas. Chest pain occurring after tumor of the lung or the mediastinum due to invasion of the pleura. Certain tumors produce characteristic types of pain. For example, back pain is seen with multiple myeloma, and severe shoulder pain and arm pain is seen with Pancoast tumors.

Key words: cancer pain, tumor-induced pain, chemotherapy induced-pain, radiation therapy-induced pain.

CLASSIFICATION OF CANCER PAIN

Patients with advanced malignancy often have pain as their chief complaint. The pain is present in 20% to 50% of all patients in early stages to 55% to 95% in the latter stages of cancer disease. Approximately 60% to 80% of all patients have tumor-related pain, 20% to 30% have treatment-related pain, and 10% to 15% have pain unrelated to the cancer. Because of its subjective nature, pain, especially chronic pain, is very difficult to classify. Pain may be classified according to its neurophysiologic mechanisms and to pain duration.

According to neurophysiologic mechanisms underlying in pain, all pain syndromes are classified as nociceptive, neuropathic, referred, and sympathetic pain. Nociceptive pain is generated by activation of ending of primary afferent neurons responsive to noxious stimuli (nociceptors) that have been situated in ending of primary afferent neurons responsive to noxious stimuli (nociceptors) that have been situated in somatic (skin, muscle) or visceral (lung, liver, intestine) tissue. Nociceptors are not found in the central nervous system. Nociceptive pain that originates from somatic structures is also termed as somatic pain; it is characterized as well-localized, sharp, aching, or pressure like. Somatic pain is carried along the sensory fibers. Pain originating from viscera is also known as visceral pain and is described as deep, dull, vague, difficult to locate, cramping or gnawing, often radiating away from the affected organ when due to obstruction of a hollow viscus, and sharp, or aching, when due to involvement of organ capsules or other mesentry. It is usually accompanied by an increase in sympathetic outflow and spasm of adjacent musculature.
Visceral pain may be transmitted by autonomic (sympathetic) fibers. Neuropathic pain is defined as pain produced by an alteration of neurological structure and/or function of neurons. Direct injury to neuronal tissue from tumor infiltration or from cancer therapies (radiation, chemotherapy) can result in this condition. A high frequency of cancer pain is associated with neuropathic pain. The main difference between neuropathic and nociceptive pain is the absence of a continuous nociceptive input. A lesion in the central nervous system causes a central neuropathic pain, such as thalamic pain, post-paraplegia pain, or post quadriplegia pain. Lesions in the peripheral nervous system produces a peripheral neuropathic pain (diabetic painful neuropathies, metastatic neuropathies). Referred pain, or viscerosomatic reflex - the pain is referred to the dermatomes represented by the spinal segments supplying the affected viscera. Sympathetic pain can occur after pathological fractures, thrombosis due to hypercoagulable states, and lymphedema of extremities. This condition is characterized by constant burning, algodystic pain with associated sudomotor and vasomotor changes, edema and coldness of the affected area.

According to duration a pain may be defined as acute and chronic pain. All pain syndromes begin as acute and remain acute during the time of the course of expected healing of the causative stimulus. Acute pain syndromes generally have either somatic or visceral nociceptive sources, but a neurogenic causa may be a component of some of them. Somatic sources of acute pain include injuries to skin, muscle, fascia, periosteum and joints. Visceral sources of acute pain include distention, stretching, inflammation, and ischemia of the peritoneum, hollow abdominal and pelvic organs, solid organ capsules, pleura, myocardium, and pericardium. Chronic pain is defined as persisting a month beyond the usual course of an acute disease or a reasonable time period for an injury to heal. Chronic persistent pain may impose severe physical, emotional, or socioeconomic influences on the patients and his relevants. Cancer pain may result from direct infiltration, or pressure, or stretching of nerve fibers. Also, it may be induced by secondary infection, for example, pyelonephritis, pyometria or aspiration pneumonia in patients suffering from tumours of the mouth, pharynx or larynx.

There may be infection within the tumour itself. Obstruction of a hollow viscus, such as the ureter in carcinoma of the bladder or cervix, can give rise to ureteric or renal colic, while the obstruction of the bowel, in gynaecological or pelvic malignancy, may produce subacute bowel obstruction and pain. Tissue damage secondary to a malignancy treatment may be a source of intractable pain, as radiation-therapy and chemotherapy-induced pain. In essence, the cancer pain may be thought of as a combination of chronic and continually recurring acute pain, but during a progression of malignancy disease a neuropathic and sympathetic pain may be accompanied.

**PAIN SYNDROMES**

**Tumor-induced pain**

Pain may occur at the site of the primary tumor or at the site of the metastasis, or it may be referred to a distant area.

Bone Pain - Bone metastasis are the most common cause of chronic pain in cancer patients. The pain is caused by endosteal or periosteal nociceptor activation on two ways: by realizing chemical mediators or by direct mechanical distortion. Direct tumor invasion into adjacent soft tissue and nerves may be also very painful.

Tumor-induced osteolytic activity produces prostanoids, specifically PGE2, which may sensitize peripheral nerve endings, thus priming the organism for nociceptive input. Other tissue autocoids are also released as a result of osteolytic activity (tumor necrosis factor, potassium, bradykinin). These tissue hormones lead to sensitization of neurons to mechanical, chemical, and thermal stimuli. They also lower discharge thresholds of the neuronal membrane, produce exaggerated responses to suprathreshold stimuli, and provoke tonic impulse discharges in normally silent nociceptors. The primary nociceptive source of input from the bone is the periesteum. Joint pain often arises as a reaction to inflammatory processes provoked by the malignant process and may be classified as a paraneoplastic syndrome.

The most frequent metastases to bone are cancers of lung, breast and prostate. The vertebrae are the most common sites of bony metastases. In the thoracic spine are located more than 30% of all vertebral metastases; lumbosacral and cervical metastases account for approximately 20% and 10%. Multiple vertebral metastasis occurs in more than 85% of patients, but some of them are very difficult for visualization. Magnetic resonance imaging (MRI) is probably the best method for imaging this microlesions. Computed tomography (CT), plain radiography, tomography and bone scintigraphy are the complementary procedures.

Metastatic destruction of the atlas or pathological fracture of the odontoid process demonstrate a typical uchaal or occipital pain, exacerbating by movement of the neck, especially by flexion. Metastases of the C7 or Th1 vertebra result in pain referred to the interscapular region. Unfortunately, a radiographic evaluation could be targeted to the painful area caudal to the site.
of lesion. Patients with interscapular pain have to undergo MRI of both the cervical and the thoracic spine. Similary, a Th12 or L1 vertebral metastases can refer pain to the ipsilateral iliac crest or the sacroiliac joint. Invasion of the sacrum is manifested by severe focal pain radiating to buttocks, perineum, or posterior thighs, exacerbating by sitting or lying and relieving by standing or walking. The metastatic invasion to surrounding structures can results in other pain syndromes. Spreading laterally to m. pyriformis, a pyriformis pain syndrome could be appeared; it characterized a pain located in buttocck or posterior leg, exacerbating by internal rotation of the hip.

Metastatic involving of the sacral plexus, may leads to a sacral neuropathic pain syndrome. Epidural compression of the spinal cord or cauda equina is the common cause of cancer pain. This pain usually precedes neurological signs by a prolonged period and should be viewed as a indicator of growing of epidural metastasis.

Because the back pain is a nonspecific symptom that can result not only from bony or paraspinal metastases, with or without epidural progression, but from many benign conditions also, a early systematic evaluation is necessary. The options for definitive imaging include MRI and CT myelography. Metastatic invasion of the pelvis commonly provokes a incidental pain by ambulation. Tumor involvement of the acetabulum or head of the femur typically produces localized hip pain radiating to the knee or medial thigh; the pain is aggravated by weight bearing and movement of the hip. Metastatic spreading in pelvic region frequently leads to compression of lumbosacro-plexus inducing chronic pain in the leg or lumbal region.

Cancer of breast, lung, and prostate frequently send metastasis in base of skull. These pain syndromes often represent a combination of nociceptive and neuropathic pain

**HEADACHE**

The prevalence of headache in patients with brain metastases is 60% to 90%. The pain may be local, at the site of tumor, or generalized. The intracranial mass lesions produced headache by stimulation of nociceptors in dural and vascular tissue. Especially the stretching of these structures are painful. Such effects of tumors may be, directly or indirectly, due by increased intracranial pressure. Maneuvers that transiently increase intracranial pressure can cause episodes of sever headache. Patients with multiple metastases and those with posterior fossa lesions are more likely to experience headache. Posterior fossa metastases often cause a bifrontal headache.

According to the site of intracranial metastatic involvement there are various pain syndromes. Parasellar syndrome supraorbital or frontal headache which may be associated with some of other neurological dysfunction (diplopia, external opthalmoparesis, quadrantanopsia). Orbital syndrome progressive pain in the retroorbital and supraorbital area and associated symptoms (blurred vision, chemosis, proptosis, external opthalmoparesis). Jugular foramen syndrome refered pain to the posterior pharynx, ipsilateral ear, mastoid region or ipsilateral neck or shoulder; occasionally, a pain may mimics idiopathic glossopharyngeal neuralgia. Occipital condyle syndrome - unilateral occipital pain worsening with neck flexion, ipsilateral hypoglossal nerve paralysis and sternocleidomastoid weakness. Clivus syndrome pain localized in vertex area and worsened by neck flexion, accompanied by dysfunction of cranial nerves (V-XII). Sphenoid sinus syndrome - bifrontal or retroorbital pain with radiation to the temporal region, diplopia and abducens paresis. Middle cranial fossae syndrome - pain in the cheek or jaw, occasionally can mimics idiopathic trigeminal neuralgia; hypesthesia in the trigeminal nerve distribution and the weakness in the ipsilateral muscles of mastication.

**VISCERAL PAIN**

Gastric cancer has a high mortality rate, especially adenocarcinoma. The clinical presentation may be asymptomatic or with vague, epigastric pain, associated with vomiting, weight loss and hematemesis. Pancreatic cancer is a lethal disease and less than 2% of the patients survive over five years. The clinical presentation is that of an epigastric, gnawing, dull, ach- ing pain that radiates to the back in 25% of the patients. It is associated with anorexia, weight loss and vomiting.

Extensive intrahepatic metastases may produce a local dull and aching pain in the right subcostal region or a referred pain in the right neck, shoulder and scapula. The nociceptive structures in the liver are the capsule, vessels and biliary tract; they are inervated from celiac plexus, phrenic nerve and lower right intercostals nerves. Early primary cancer of the pelvic viscera rarely produces pain. Its initialy spread to lumbosacral plexus and bones leading to intensive pain. Retroperitoneal and pelvic lesions involving the deep somata structures of the posterior abdominal wall, the sensitive connective tissue or the celiac plexus may produce mixed nociceptive and neuropathic pain. The pain is dull and located in the epigastrium and the low thoracic region in the back. It is exacerbated by movement or deep inspiration, and improved by sitting or lying in a lateral decubitus position.
The abdominal and pelvic cancers may produce the continuous or colicky pains as a result of chronic intestinal obstruction with consecutive intestinal distension, mesenteric tension, and mural ischemia. The pain is referred to the dermatomes represented by the spinal segments supplying the effected viscera. Peritoneal carcinomatosis can cause a diffuse abdominal or low back pain or stretching pain in the anterior abdominal wall. Malignant tumors of the colon, rectum, female reproductive tract, and distal genitourinary system cause a perineal constant or aching pain, often aggravated by sitting or standing. It may involve mixed nociceptive or neurapthic mechanisms. In patients with urinary, colonic, or gynecological carcinomas, involvement and compression of lumbosacral plexus (L5-S1) produces pain in the anterior thigh, or at compression of upper lumbal plexus (L1-L3) pain is located in the groin. At the lower lumbal plexus compression, pain is distributed from the posterior part of the leg to the heel. Metastatic involvement of sacral plexus is characterized by perineal sensory loss associated with dull, aching, medline pelvic pain.

Cancers of the cervix, ovary, prostate, and rectum are most commonly associated with a typically dull chronic discomfort in the flank, which may radiate into the inguinal region or genitalia. In advanced stages of malignant disease a infiltration and compression of lumbar plexus produces pain in the anterior thigh, or at compression of upper lumbal plexus pain is located in the groin. At the lower lumbal plexus compression, pain is distributed from the posterior part of the leg to the heel. Metastatic involvement of sacral plexus is characterized by perineal sensory loss associated with dull, aching, medline pelvic pain.

Pancoasts syndrome is present when a carcinoma at the lung apex makes invasion and erosion of one or more of the upper ribs, expanding directly into the brachial plexus. As a result of involvement of the brachial plexus these patients suffer very severe pain irradiating into shoulder, the ipsilateral upper extremity, medial two fingers and medial upper arm, adjacent thorax, or scapula, with or without neurological physical signs. The pain is characteristically persistent. Clinical signs, as Horner’s syndrome, sympathetic denervation and sensory or motor involvement of the lower brachial plexus, are present in 34% of these patients.

**RADIATION THERAPY**

**INDUCED PAIN**

Postradiation pain may occur after few weeks, months or years of radiation therapy as neuropathic pain or as nociceptive pain (the rectum and rectosigmoid are more commonly involved). Postradiation plexopathy of brachial, cervical, or lumbosacral nerve plexuses is accompanied by diffuse, constant, burning neuropathic pain with dysesthesias and paresthesias developing from 6 months to 20 years after therapy.

Early after irradiation may develop a painful mucosal thinning or ulceration of oral, gastric, esophageal or some other mucosa. The rectum and rectosigmoid are more commonly involved. The damage of small intestine lead to cramping pain, mucosal ulcer and development of fistula. Sometimes, after three months to three years appear a chronic cramping pain of proctitis caused by radiation therapy.

Postradiation myelopathy can be expressed as transient or as chronic form. The first develops over 4 months after radiation and resolves in 2 to 36 weeks. The second develops over 5 to 13 months after radiation.

**CHEMOTHERAPY**

**INDUCED PAIN**

The oral mucositis, as a sequela to chemotherapeutic agents, is making a swallowing very difficult. The chronic steroid use frequently leads to aseptic necrosis of bone or pathological fracture of the femoral or humeral head which are associated with constant, intractable dull pain. Some of the used chemotherapy agents may result in the development of chronic pain.

Treatment of cancer pain with therapeutic doses of vincristine and vinblastine can result in a painful symmetrical polyneuropathy, arthralgia and myalgia.

**REFERENCES**

