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Short Commentary

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Cancer metastasis - A molecular insight and the challenges during covid times

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Introduction

The word Metastasis means 'Meta-transformation, stasis-residence', is stated as the spread of cancer by invasion in a way that is discontinuous to the primary tumor mass and forms secondary tumor masses in a distant area at the site of lodgment. Metastasis is a feature to distinguish malignant from benign tumors [1,2]. Worldwide, 19.3 million new cancer cases arise and about 10.0 millions of cancer deaths has occurred in 2020 [3]. In the year 2020 1,392,179 cases of cancer were reported in India, among which the breast, lung, mouth, cervix uteri, and tongue were the most commonly involved site. The head and neck, stomach, breast cancers are diagnosed in their locally advanced stage whereas, distant metastasis was predominant in lung cancer. Thus metastatic potential differs among the different type of cancer [4].

About 30% of patients with newly diagnosed solid tumors (other than melanomas) presents with clinically evident metastases. About 20% have hidden metastases at the time of diagnosis. It is stated that metastasis is the main cause for 90% of cancer deaths [1,2,5].

Origin of metastatic cascade [5]

A number of components are stated in initiating the metastatic cascade which includes

1. Epithelial to Mesenchymal Transition
2. Stem cell origin
3. Macrophage Facilitation of Metastasis
4. Myeloid Cell Origin

1. Epithelial to Mesenchymal Transition (EMT): EMT states that the metastatic cells arise from epithelial stem cells or differentiated epithelial cells. These epithelial cells transform into a tumor cell with mesenchymal features.
2. Stem cell origin: The biological characteristics, gene expression are often similar to both the stem cells and cancer cells. That both the tumor and stem cells use anaerobic energy for metabolism. Supporting this, evidences suggests that cancer is a metabolic disease that involves respiratory insufficiency with compensatory mechanism. Another reason is that as stem cells have the ability to proliferate and migrate which are features of malignant cell as well.
3. Macrophage Facilitation of Metastasis: Macrophages, the innate immune cells on differentiation are equipped to sense and respond to infections and injuries, by playing an important role in homeostasis and repair. Many malignant tumors contain more numbers of macrophages, which are termed as Tumor Associated Macrophage has the ability to establish the premetastatic niche, by enhancing tumor inflammation and angiogenesis that facilitates the metastatic cascade.
4. Myeloid Cell Origin: Metastatic cancers arise from respiratory insufficiency in myeloid cells or their lineage descendants. The hypothesis states that the metastatic cancer cells arise directly from cells of myeloid origin or by hybrid cells due to the fusion of macrophages and non-metastatic stem cells.

The metastatic cascade [1,2,5-8]

The Cancer cells detach from the primary tumor, intravasate into the systems of circulatory and lymphatics, evade immune attack, and extravasate at distant capillary beds, then invade and proliferate to distant organs. They also establish an environment that facilitates angiogenesis and proliferation, resulting in malignant secondary tumors.

The first step in the spread of is the development of rapidly proliferating clone of cancer cells. The Normal cells remain adhered to each other because of the presence of cell adhesion molecules E.g., E (epithelial)-cadherin. In epithelial cancers, there is loss or inactivation of these E-cadherins and other cell adhesion molecules which results in loosening of tumor cells. Their function is lost either by mutational inactivation or activation of the genes or by inappropriate expression of transcription factors, which causes suppression of E-cadherin expression. The cancer cells are thus loosened. The Loosened cancer cells will become attached to the ECM proteins (E.g.,: laminin and fibronectin) Following which degradation of the basement membrane and interstitial connective tissue in certain areas occur. The Tumor cells either by itself secrete proteolytic enzymes or induce other stromal cells to induce proteases. Overexpression of degrading enzymes and its inhibitors are decreased. Overexpression of the enzymes contribute to the dissolution of ECM and then make way for tumor cells to pass through the interstitial matrix. Different families of proteases, MMPs, cathepsin D, and urokinase plasminogen activator, are implicated in tumor invasion. After degrading the basement membrane the tumor cells migrate into lumen of capillaries or venules. Migration involves many receptors and signaling proteins that eventually act on the actin cytoskeleton. The movement of the tumor cells are directed by Autocrine motility factor (AMF), a cytokine derived from the tumor cells. Cleavage products of the matrix components which are formed following degradation of ECM have properties of tumor cell chemotaxis, growth promotion and angiogenesis in the cancer. The Stromal cells produce paracrine effectors of cell motility, (E.g., hepatocyte growth factor) binds to the receptors on tumor cells. The tumor cells in the lumen are covered with constituents of the blood and form the thrombi. In bloodstream, some of the tumor cells form emboli by attaching and adhering to the circulating leukocytes and platelets. The aggregated tumor cells thus obtain protection from the host cells. This Thrombus provides nourishment to the tumor cells and they also protects them from the immune attack by the host cells. The tumor cells or tumor emboli adheres to the vascular endothelium, by egress through the basement membrane into the organ by mechanisms similar to invasion. The extravasated malignant cells on lodgment especially in the right environment grows further by the influence of growth factors that are produced by tumor cells by itself, hosts, and by cleavage products of matrix.

Role of immune cells [9]

At least 25% of cancers associated with Chronic inflammation which is a critical hallmark of cancer. The presence of immune cells in most human tumors, are characterized as features of cancer progression.

Neutrophils

Neutrophils are among the first immune cells thatare recruited to the damaged tissue, where they eliminate pathogens and modulate the inflammation, high levels of Tumor Associated Neutrophils are been seen in cancer cases. The recruitment of neutrophils to the Tumor Microenvironment is mediated by CXCR2 ligands that are secreted by cancer and stromal cells. Tumor Associated Neutrophils contribute to angiogenesis by secretion of the required factors.

Natural killer cells

Natural Killer cells, the innate immune cells display rapid cytolytic activity in response to the transformed cells. NK cells have a wide array of cell surface receptors that are used for immune surveillance. The receptors target cancer cells that lack MHC-I, and marks them for programmed cell death. They kill the tumor cells by releasing cytotoxic perforin and granzyme, and also triggers the apoptotic pathways in tumor cells.

Dendritic cells

Dendritic cells are specialized antigen-presenting cells which

represent the interface between innate and adaptive immunity and presents the endogenous and exogenous antigens to T cells in the context of MHC molecules. DCs recognizes and stabilizes interaction with dying cancer cells followed by maturation, engulfing, and antigen presentation in cancer.

Routes of metastasis [1,2]

Cancers may spread to distant sites by following pathways:

1. Lymphatic spread

2. Hematogenous spread

3. Spread along body cavities and natural passages (Transcoelomic spread, along epithelium-lined surfaces, spread via cerebrospinal fluid, implantation).

1. Lymphatic spread

In general, carcinomas metastasize by lymphatic route whereas sarcomas byhematogenous route. Sometimes, sarcomas may also spread by lymphatic pathway.

The lymph nodes involvement by malignant cells may be of two forms:

a) Lymphatic permeation- The walls of lymphatics are invaded by cancer cells and can form a continuous growth in the lymphatic channels.

b) Lymphatic emboli -The malignant cells detaches to form tumor emboli and is carried along the lymph fluid to the next draining lymph node.

Regional nodal metastasis

Regional lymph nodes drain the tumourare involved in regional nodal metastasis. E.g., Carcinoma breast metastasises to axillary lymph nodes, Carcinoma thyroid metastasises to lateral cervical lymph nodes, bronchogenic carcinoma metastasises to hilar and para tracheal lymph nodes. However, all the regional nodal enlargements are not due to nodal metastasis as the necrotic products of tumor and its antigens can produce immunologic responses in the nodes causing hyperplasia of the follicles, which is termed as lymphadenitis and proliferation of macrophages into the subcapsular sinuses termed as, sinus histiocytosis.

Skip metastasis

Sometimes the lymphatic metastases does not develop first in the lymph node nearest to the tumor as of the venous lymphatic anastomoses or can be due to obliteration of lymphatics by inflammation or radiation.

Retrograde spread

Obstruction of lymphatics by tumor cells causes the lymph flow to be disturbed and the tumor cells spread against the flow of lymph by causing retrograde metastases to unusual sites. E.g.., Carcinoma prostate Metastasise to the supraclavicular nodes, bronchogenic carcinomas metastatic deposits to the axillary lymph nodes.

Virchow's node

Virchow's lymph node, a nodal metastasis preferentially to the supraclavicular lymph node from cancers of the abdominal organs E.g., cancer of stomach, colon, and gall bladder.

2. Hematogenous spread

Blood-borne metastasis is a common route for the sarcomas. But certain carcinomas also tend to frequently metastasize by this mode of spread, especially by those of thyroid, breast, kidney, liver, prostate and ovary.

The blood-borne metastasis commonly occurs in: The brain, lungs, liver, bones, kidney and adrenals. Systemic veins drain the blood into vena cava from the limbs, head and neck and pelvis. Hence, cancers of these sites more often metastasize to the lungs. Portal veins drain the blood from the bowel, spleen and pancreas into liver. Hence, tumors from these organs frequently have secondaries in the liver.

Arterial spread of tumors is less frequentasthe arteries are thick-walled and contain elastic tissue which are resistant to invasion. Nevertheless, arterial spread can occur when the tumor cells pass through the pulmonary capillary bed or through pulmonary arterial branches that have thin walls. Cancer of the lung may, however, metastasize by pulmonary arterial route to kidneys, adrenals, bones, brain etc.

3. Spread by body cavities

Uncommonly, some cancers may spread by seeding across the body cavities and natural passages.

Transcoelomic spread

Certain cancers invade through serosal wall of coelomic cavity so that clusters of tumor cells or tumor fragments break off to be carried in the coelomic fluid and get implanted elsewhere in the body cavity. Peritoneal cavity is often involved, but occasionally pericardial and pleural cavities are also affected.

Covid and caner patients

Liang et al. stated that cancer patients have a higher requirement for intensive level of care, mechanical ventilation and death, when compared to non-cancer patients. If the patient is asymptomatic, laboratory testing and imaging should be postponed for months. In case of symptomatic patients, or high suspicion for disease recurrence the physicians should decide considering the comorbidities, patient conditions and tumor biology. New cancer diagnosed patients experience the most distressing times during this period. Liang suggested postponing the chemotherapy or surgery in stable cancer patients during this period especially in endemic areas. However, Zhang et al. was recommended the chemotherapy should not be withheld or postponed in order to reduce the risk of infection in the current situation. Vishal J et al recommends adjuvant chemotherapy for early stage cancer during this COVID-19 period. As there is a higher risk of transmission of infection as the patients are immunocompromised, extreme measures to decrease the spread of COVID-19 should be maintained [10].

Conclusion

As most of the cancer patients are immunocompromised, there is a higher chance of getting exposed to covid during their hospital visits which can be fatal as well. This pandemic may end now or later. Treating a cancer patient in time has a better role in prognosis and the patients life expectancy. Delay in diagnoses or treatment can be lethal and may have a compromised state of life. Proper guidance should be given by professional bodies for the cancer patients and people taking care of them to reduce the fear of cancer and its treatment.

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