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Emperipolesis in neuroendocrine tumors of the thymus

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ABSTRACT

Emperipolesis is a biological phenomenon of rare origin and is characterized by a process in which a cell penetrates another living cell. In contrary to phagocytosis where the engulfed cell is killed or neutralized by lysosomal enzymes of the macrophage, in emperipolesis, the cell exists as a viable cell within another. Moreover, this cell can exit at any time without any structural or functional abnormalities for either of them. The process of emperipolesis is seen in many physiologic and pathophysiologic conditions. In this article we focus on the occurrence, pathogenesis and appearance of emperipolesis in the neuroendocrine tumors of the thymus. Moreover, we highlight the possible diagnostic and future therapeutic strategies in the treatment of thymic tumors.

INTRODUCTION

Neuroendocrine tumors of the thymus are classified according to World Health Organization (WHO) guidelines. Primary neuroendocrine tumors of the thymus (NETTs) are very uncommon and represent less than 5% of mediastinal and thymic neoplasms. They account for only 0,4% of all neuroendocrine tumors (Dinter, 2019). NETTs are classified according to WHO criteria into lowgrade typical carcinoids, intermediategrade atypical carcinoids (ACs), and two highgrade malignancies, large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SCC) (Dinter, 2019). To categorize tumors, morphology evaluation should be performed, with the assessment of parameters such as organoid nesting, rosette formation, peripheral palisading of tumor nests, and trabeculae (Dinter, 2019). This classification was made by determining the mitotic activity, cellular atypia and areas of necrosis (Moran, 2000). To classify a tumor as a typical carcinoid, it is identified to have no necrosis and a size of 0,5 cm or greater, AC is reported to have 2 to 10 mitoses per 2 mm with or without necrosis, whereas LCNEC and SCC have number of mitoses greater than 10 per 2 mm (Moran, 2000). According to this classification, AC and LCNEC are the most common subtypes in the thymus (Dinter, 2019).

The 3rd and 4th edition of the WHO Classification of thoracic tumors are considered to be most important. In accordance with the 2004 classification, WHO distinguishes A, AB, B1, B2 and B3 types of thymomas and thymic carcinomas and other seldom ones. (Marx, 2014; Petrini, 2014). The fourth edition is expanded to include an interdisciplinary perspective and improves histological and immunohistochemical diagnostic criteria in order to increase the diagnostic repeatability.

The nomenclature of the major thymoma types was retained in the 4th edition, as well as Masaoka-Koga system for the staging of thymomas (Marx, 2015). However, the term "combined NETTs" is no longer used, excluding type AB thymoma. Instead, there is a requirement to include all histologically diagnosed thymoma types, starting with the most important ones and quantified in 10% increments (Marx, 2015).

Primary neuroendocrine tumors of the thymus (NETTs), which include thymic neuroendocrine tumors, thymoma (TM) and thymic carcinoma (TC) are always considered to be malignant, and it is unrelated to subtype or histology of the tumor (Jeong, 2020; Marx, 2015).

In the past there was a problem with distinguishing between some thymoma subtypes and thymic carcinomas, because of morphological overlapping (Marx, 2014). Diffe-rences between thymomas and thymic carcinomas have been diagnosed by epigenetic and genetic methods and transcriptomic analyses, which showed different methylation patterns, expression profiles of antiapoptotic genes and specific mutations of epigenetic regulatory genes (Marx, 2015). Thus, interobserver reproducibility has been improved. Also point mutation in the GTF2I (general transcription factor 2-I) oncogene in all major thymoma subtypes and thymic carcinomas was observed, which indicates the common origin of the NETTs (Petrini, 2014).

The possible role of emperipolesis in neuroendocrine tumors of the thymus requires further clarification. In this review we discuss the previous findings in this area of expertise and the significance of this rare process, not much reported in the literature.

SEARCH STRATEGY AND SELECTION CRITERIA

The authors reviewed data published in 3 languages: English, German, and Polish between 1989 and 2020. Data were collected using keywords such as emperipolesis, entosis, and neuroendocrine tumors of the thymus. The following scientific databases such as PubMed, Google Scholar, Borgis, MEDLINE, and Cochrane Library were used to search for articles. The selected articles focused on determining the importance of emperipolesis in the pathogenesis, diagnosis and treatment of thymic neuroendocrine tumors. The number of articles selected was 54. In addition, this work was enriched with 7 manually selected materials that were related to the discussed topic. The strategy was aimed at presenting yet not entirely understood aspects of emperipolesis in the context of neuroendocrine tumors of the thymus as well as emperipolesis itself from various perspectives.

WHAT IS THE EMPERIPOLESIS?

Emperipolesis is characterized by the presence and movement of one cell within the cytoplasm of another. Emperipolesis is strictly related to cell-in-cell phenomenon, which can be associated with the prognosis of cancers (Wang, 2019). Histopathological screening shows an absorbed cell in a membrane-bound vacuole in the host cell. On occasion absorbed cells may continue to live for a short period of time after absorption. It is possible for an internalized cell to escape from the host cell, and it can survive after this process (Gupta, 2017).

The term "*emperipolesis*" originates from the Greek (*em* – inside; *peri* – around; *polemai* – wander about) and it was first reported and defined in 1950 as the active penetration of one cell by another (Humble, 1956). Wang and Li (2019) had discovered that emperipolesis can mediate natural killer cell-mediated tumor cell death, but requires membrane fluidity of the target cell, so that the interaction with natural killer cells could occur. The host tumor cell disintegration is preceded by lysosome-mediated degradation pathway after the emperipolesis (Xia, 2008). According to Overholtzer's report, natural killer cells sometimes can undergo mitosis inside the host tumor cell after emperipolesis and that indicates the further fate of heterogeneous cells in killer cell-tumor cell emperipolesis (Overholtzer, 2007).

Rosai-Dorfman disease (RDD) is a pathological condition in which emperipolesis occurs. It was first observed by Juan Rosai and Ronald Dorfman in 1969, and has been diagnosed by cervical lymphadenopathy, lymph node sinuses and emperipolesis that occurred within histiocytes (Rosai, 1969). In RDD a dense histiocytic infiltrate with emperipolesis is present. The infiltrate contains associated lymphocytes, plasma cells, and neutrophils (Cangelosi, 2011). However, emperipolesis is a diagnostic feature only when S100 protein is expressed in histiocytes (Juskevicius, 2001). Yet, due to variable morphology characteristics in xanthogranulomatous diseases, emperipolesis is the most important histologic feature in distinguishing it from RDD disease (Cangelosi, 2011).

CHARACTERISTICS OF THYMIC NEUROENDOCRINE TUMORS

Primary neuroendocrine tumors of the thymus (NETTs) belong to the group of tumors with high aggressiveness (the ability to form metastases in more than 80% of patients) and a relatively low incidence (Chaer, 2002; Filosso, 2017). NETTs account for only about 0,4% of all carcinoids and less than 5% of all the anterior mediastinal neoplasms (Yao, 2007; Filosso, 2017). Primary neuroendocrine tumors of the thymus are found predominantly in males, with a male to female ratio of 3:1 (Moran, 2000). They are most common in white males and are typically seen in the fourth or fifth decades of life, with an average age of onset of 58 years (Gaur, 2010). NETTs likely arise from Kulchitsky cells and localize primarily to the anterior mediastinum (Berman, 2020).

According to the WHO (2015), primary thymus neuroendocrine tumors are classified into two main histopathological types: well-differentiated (typical and atypical carcinoids) and poorly differentiated (small cell and large-cell neuroendocrine crayfish) (Travi, 2015).

Clinically, NETTs may manifest as follows: 1. asymptomatic, coincidentally detected on chest radiography for other reasons; 2. with symptoms due to displacement/compression/invasion of mediastinal structures; 3. associated with endocrinopathies; or 4. with symptoms due to

distant metastases, most commonly to the liver, brain, lung, or bone.

Primary neuroendocrine tumors of the thymus give many non-specific symptoms including chest pain, cough, dyspnea, superior vena cava syndrome, lingual nerve palsy, and diaphragmatic elevation due to damage to the phrenic nerve (Berman, 2020). In addition, half of the patients had lymph node involvement, but with no proven effect on reducing treatment efficacy (Filosso, 2017).

Approximately 50% of thymic neuroendocrine tumors are functionally active and have the ability to secrete hormones. Ectopic secretion of ACTH and serotonin can lead to paraneoplastic Cushing's syndrome and carcinoma, respectively. Less commonly, excessive secretion of somatoliberin (GHRH, growth hormone-releasing hormone) or growth hormone (GH) has been described, which can cause acromegaly (Melmed, 2009). People with hypertension, heart failure, diabetes, and arthropathies are primarily at risk of developing this condition (Bolanowski, 2014).

In addition, 25% of patients struggling with a thymic tumor have a coexistence of multiple endocrine neoplasia type 1 (MEN1) syndrome; one of the 8 contemporary multiple endocrine neoplasia syndromes (Gietka-Czernel, 2017). MEN1 is the leading cause of death among patients with thymic neuroendocrine tumors (Phan, 2010). Therefore, many authors recommend prophylactic thymic resection (parathyroidectomy) in patients with MEN1, which reduces the risk of cancer during life (Teh, 1998; Trump, 1996)

IMAGE OF EMPERIPOLESIS IN EPITHELIO-RETICULAR CELLS OF THYMIC TUMORS

Most thymic tumors have thymic epithelial cells that do not show cytological malignancy. Moreover, these cells are mixed with lymphocytes in different proportions (Verley, 1985; Lewis 1987). It appears, that the phenomenon of lymphatic emperipolesis, in which the intact cell is present in the cytoplasm of the larger cell, may occur in epithelioreticular cells. This issue however warrants further scientific evaluation. The subject of the thymoma in the context of emperipolesis is likewise not much reported in the literature.

In an ultrastructural study, Llombart-Bosch suggested that close contacts existed between the thymic lymphocytes and the epithelioreticular cells. This appearance was suggestive of emperipolesis (Llombart-Bosch, 1975). In another research conducted by Izard, the cytoplasmic structures resembled the embryonic epithelioreticular cells in the guinea pig thymus (Izard, 1966). Interestingly, Llombard-Bosch suggests that mitotic lympho-cytes are found throughout the tumor near E-R cells (epithelioreticular cells). Moreover, there is a morphological and lymphocytic death relationship, while the lymphocytes were in the cytoplasm of E-R cells. The onset of such necrosis is progressive nuclear pycnosis and secondary chromatolysis. By the time the cytoplasm was completely gone, the fatty degeneration and the mitochondrial vacuolization had started. The remaining monoliform reticular particles swallowed mesenchymal macrophages. Such cells were characterized by advanced degradation (Llombard-Bosch, 1975). Macrophages have the ability to phagocytose and to absorb what they phagocytize. They are classified as connective tissue and are associated with the body's defense mechanisms (Cichocki, 2002). In this case, the mesenchymal macrographs were randomized in the tumor stroma, but were more frequent near E-R cells. Moreover, phagocyte-ingested cell debris of lymphocytic origin were also present (Llombard-Bosch, 1975).

There are only very few publications on emperipolesis in the context of the thymus gland, and even less in relation to E-R cells. It seems that the topic of emperipolesis requires further attention and research. Similar observations to the two cases cited above were noted in epithelionreticular cell thymoma in carp. Lymphocytes were taken up by E-R cells. It therefore seems logical that there is some kind of cytoplasmic communication system between lymphocytes and E-R cells. Such a phenomenon can take place in the human thymus, as indicated by Golditeinand MacKay (1969) (Romano, 2004).

It is important to properly distinguish between thymoma and T lymphoblastic lymphoma using needle biopsy as this has serious consequences in further treatment. Among diagnostic criteria, a factor that favors thymoma is the demonstration of increased numbers of keratin-positive epithelial cells using immunohistochemical staining. Loss of keratin expression in neoplastic epithelial cells could lead to detrimental misdiagnoses (Adam, 2014). Notably, false-positive

or otherwise negative results of various tests may be related to the physiology of the cell itself, which may lose or gain certain properties under the influence of given factors or for unexplained reasons. Here the loss of keratin expression is observed. The research revealed that thymic epithelial tumors showed highly reduced expression of at least one keratin (Adam, 2014).

Moreover, emperipolesis in the form of thymocytes in the cytoplasm of epithelial cells was noticed in imprint cytology but was not noticed in a histological examination, which will be discussed in the next section (Nerurkar, 2000).

According to the research, emperipolesis was also noticed in an 83-year-old patient who underwent Chamberlain anterior mediastinotomy. The presumptive diagnosis was a thymic tumor versus lymphoma. It was suggested to consider the test sample as an atypical thymoma. Another suitable alternative might be a thymic carcinoma (Mackay, 1985).

Considering the aforementioned results, the image of emperipolesis in the thymus is rarely observed, and if it is noticed, it arouses curiosity. This phenomenon warrants further evaluation. The research on animals (guinea pig and carp) is aimed at high-lighting the importance of a holistic approach to the issue. Similar studies in animals can possibly be done faster, easier and in a larger population. Results may emerge sooner, and the similarities between the human thymus and animal glands, which already have been demonstrated.

EMPERIPOLESIS AS A KEY FEATURE IN IMPRINT SMEARS OF THE THYMUS

Among diagnostic imaging of the thymus, imprint cytology has not received much attention, because the organ is rarely sampled in routine surgical practice.

It appears that emperipolesis may not be noticed on histology, but, surprisingly in imprint cytology. Based on the presented research, a fragment of the thymus was mistakenly sampled as a pretracheal lymph node in order to exclude metastasis. Interestingly, the presence of thymocytes in the cytoplasm of thymic epithelial cells (emperipolesis) was the most significant feature in the imprints (Nerurkar, 2000). Imprint cytodiagnostic is useful, for example, in examining breast tumors. Contrary to histopathology, which is more time-consuming, imprint smear can take less than an hour. Moreover, imprint smear can do amastigotes that take a short course without the need for a pathologist (Sousa, 2014). In the study of Nerurkar, the emperipolesis was based on the ingress of thymocytes into the TNC. TNCs are thymic nurse cells, which are epithelial cells in the thymic cortex, nourish the thymus and can surround the thymocytes to form lymphoepithelial complexes. Importantly, the thymocytes in the cytoplasm in this case did not show signs of nuclear degeneration. So, for example, pyknosis did not occur (Nerurkar, 2000). Pyknosis is the process of a cell in apoptosis or necrosis and consists of irreversible chromatin condensation (Kroemer, 2009). Additionally, immunohistochemistry with keratin, which confirmed that thymocytes are double by TNC. The method also showed that thymocytes are alive but not proliferating. Such emperipolesis took place not only in the cortex, but also in the corticomedullary junctions (Nerurkar, 2000). Other scientists studying immunohistochemical characterization of nurse cells in normal human thymus had similar observations. Moreover, this study showed that internalized thymocytes retain their proliferative potential (Dispasquale, 1991). Imprint smear is a quick diagnostic method, e.g. for tumors, but the disadvantage is that it does not allow reliable results in the context of tumor infiltration (Mehar, 2014).

Among the available imaging techniques, observations with an electron microscope and phase contrast microscope are indispensable for distinguishing emperipolesis from phagocytosis (Shamoto, 1980). This can be more difficult to observe under a light microscope (Mackay, 1985).

Indisputably, a wide range of diagnostic methods is needed to fully diagnose and investigate a given tumor. Paradoxically, it appears that imprint cytology, being less advanced technique than fine needle aspiration (FNA) cytology or histology, enables demonstration of such rare phenomenon as emperipolesis. More studies are necessary for these findings to be placed in a proper perspective.

COMPARISON OF EMPERIPOLESIS AND ENTOSIS

Emperipolesis and entosis are very similar processes but differ in the pattern of action and the mechanisms involved. In the case of entosis, the predominant fate of internalized cells is

lysosomemediated degradation and non-apoptotic cell death (Peng Xia, 2008). Emperipolesis, on the other hand, is the process of entry and temporary 'storage' of one cell in the cytoplasm of another cell, but one that is histogenetically foreign. In emperipolesis, a cell exists as an intact living cell in the cytoplasm of another and can exit at any time without any structural or physiological abnormality for either (Amita K, 2011). Emperipolesis is thought to improve cell survival and help prevent cell apoptosis in the host cell. The engulfed cell can be destroyed and depending on its mode of death, there are different terms to describe this procedure. For example, non-apoptotic death can occur as a result of so-called "suicidal emperipolesis" (Benseler et al., 2011). Emperitosis (a combination of emperipolesis and apoptosis) can also occur. The host cell can also be destroyed; killing of lymphocyte-containing tumor cells has been observed (Wang et al., 2013).

Both emperipolesis and entosis require extracellular free calcium and adhesion molecules and an actin-based cytoskeleton (Peng Xia, 2008). To systematically define emperipolesis and entosis it is necessary to identify the key intercellular junction molecules involved in these processes.

Entosis – from the Greek "*entos*" – "within", involves the absorption of one cell by the vacuolar system of a neighboring cell of the same type, from the same population, due to the loss of linkages between the cell and the extracellular matrix. Nonapoptotic death of such a cell may then occur, in the absence of caspase-3, requiring autophagy by lysosomal enzymes, or it may divide and leave the parent cell by a transcytosis-like movement. It is suggested that entotic cell death should be defined as a new type IV cell death.

Entosis can occur under physiological as well as pathological conditions. As a result of entosis of tumor cells, the tumor cell may undergo:

- incomplete heterophagocytosis with removal of the remaining cancer cell outside the phagocyte or complete heterophagocytosis;
- pseudo-cannibalism – no change in the tumor cell;
- disintegration into glandular bodies, which remain in the cytoplasm of the cell;
- malignant transformation, i.e. benign tumor cell becoming malignant;
- progression of the malignant tumor cell;
- suppression of the tumor process by repeated uptake of the malignant tumor cells.

PATHOGENESIS OF ENTOSIS

Entosis is caused by cell detachment from the extracellular matrix and also enhanced by an imbalance in actomyosin contraction between neighboring cells. Entosis is mediated by E-cadherins and P-cadherins increasing cell adhesion in the absence of integrin signaling. The process also requires Rho GTPase, Rho kinase ROCK and myosin-based contractile force.

Moreover, entosis is favored by the presence of the Kras oncogene and the expression of epithelial cadherins E and P. Oncogenic transformation and mechanical deformability of the cell promotes the ability to engulf other cells, which usually leads to non-apoptotic death of such cells, but may also increase the metastatic potential of the tumor and induce changes in cell ploidy, leading to the formation of binucleated cells in culture (Gupta N., 2017).

Recent studies have shown that entosis can occur even when cells are attached to the matrix. It is presumed that mitosis is then the inducer of entosis. Also, it is thought that the lack of glucose in the growth medium may induce it by increasing the activity of AMP protein kinase (AMPK) (Xinlong Wang, 2019).

PATHOGENESIS OF EMPERIPOLESIS

Emperipolesis can be physiological, pathological or a pathognomonic feature of certain diseases. It is thought to be a form of temporary cell protection against carcinogens and chemotherapeutics, as this process is often seen in some mesenchymal tumors (multiple myeloma, acute and chronic leukaemia, myeloproliferation) and also during the use of cytostatic drugs. In pathological states it also occurs in Rosai Dorfman disease, which is a histiocytic proliferative disorder in which emperipolesis can be observed in lymph nodes with inflammatory infiltration and in cerebrospinal fluid. Emperipoietic erythroblast activity in the liver has been found to increase during periods of high

hepatic erythropoietic activity and relatively anemic fetal state.

Physiological findings include emperipolesis of erythroblasts by megakaryocytes in the fetal liver, emperipolesis of lymphocytes by human glial cells in the brain.

Free calcium molecules and adhesion molecules are important in emperipolesis, as well as the actin- and ezrin-based cytoskeleton (Xia, 2008). Emperipolesis has been shown to decrease by inhibiting actin polymerisation (Takeuchi, 2010). Abnormal P-selectin located in the demarcation membrane system of neutrophils and megakaryocytes has been proposed as a cause of emperipolesis in marrow fibrosis (Centurione, 2004). It is thought that also a lymphocyte function-related antigen-1 (LFA-1 or CD11a/CD18) that can mediate intercellular interactions between leukocytes and non-blood cells together with its ligand, intercellular adhesion molecules 1 (ICAM- 1/CD54), may be associated with emperipolesis (Reina and Espel, 2017).

Emperipolesis and entosis are two different phenomena. The process of emperipolesis occurs with the involvement of Ezrin, LFA-1 and ICAM-1. The engulfed cell can escape from the host or be killed. The host cell can be destroyed by the engulfed cell. In contrast, entosis is homotypic, in which E-cadherins and P-cadherins, the Rho-ROCK-actin/myosin pathway and actomyosin contraction imbalance play important roles. The absorbed cell may be killed or survive (Xinlong Wang, 2019).

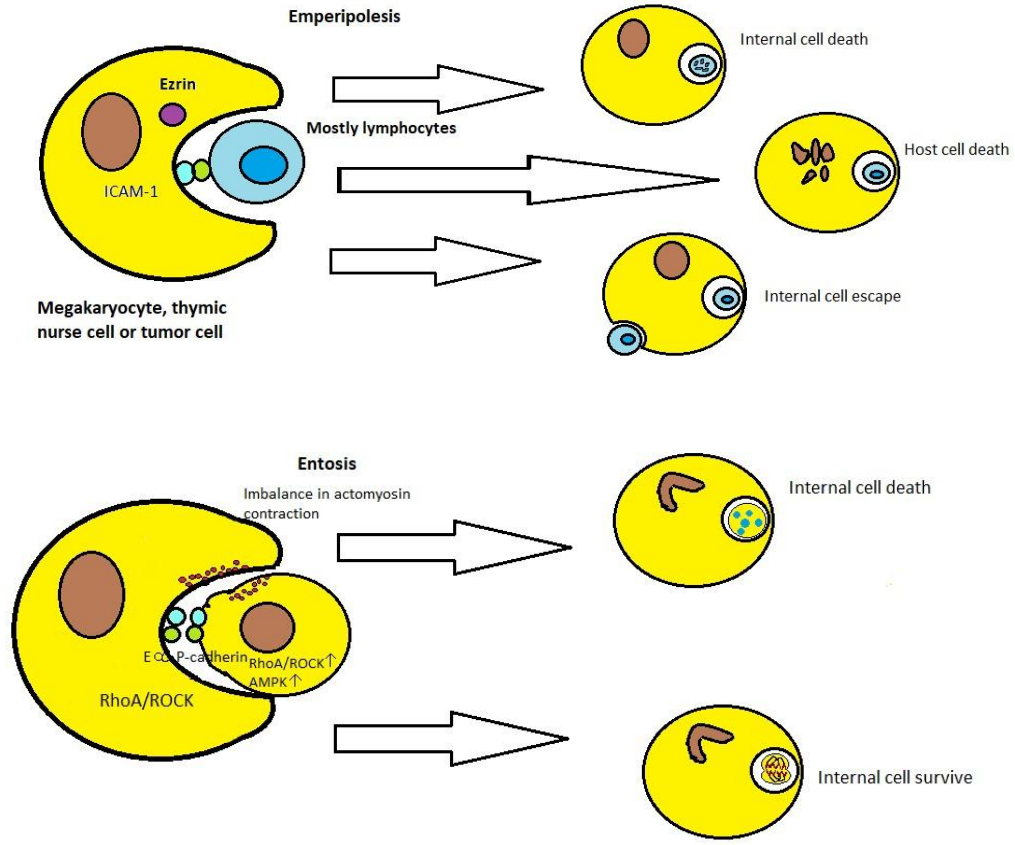

Figure 1. Emperipolesis and entosis – modified based on Wang et al. 2019

DIAGNOSIS OF NEUROENDOCRINE TUMORS

The standard procedure for the diagnosis of primary neuroendocrine tumors of the thymus is the combined use of anatomical and functional methods, since a single test technique has insufficient sensitivity and specificity (Ricke, 2000; Kaltsas, 2004).

The most commonly used diagnostic techniques for NETTs include anatomical examinations such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) (Kaltsa, 2004).

The image of NETTs in CT is non-specific and takes the form of a large, clearly delimited tumor mass with a heterogeneous signal intensity. CT allows the identification of possible cystic lesions, necrosis, hemorrhage or hemorrhage within the tumor (Xiang, 2010). In an MRI scan, thymic tumors take the form of emerging tumor masses, which also show a heterogeneous signal intensity and allow the detection of cystic lesions. MRI scan is crucial in excluding possible tumor infestation into adjacent mediastinal structures (Berman, 2020; Xiang, 2010).

In turn, functional techniques, scintigraphic studies are used, which are based on a specific connection of synthetic somatostatin analogues labeled 111In or 99mTc with transmembrane-helial receptor protein – scintigraphy of somatostatin receptor (SRS) (Krenning, 1989). The somatostatin receptors' presence in the neoplastic tissue justified the use of 111-Indium-diethylenetriamine pentaacetic acid-D-phenyl-alanine-octreotide (Octreoscan) scintigraphy, both in preoperative and in follow-up settings (Filosso, 2017).

Good quality imaging studies are the fundamental elements in establishing the starting point of primary neuroendocrine tumors of the thymus in assessing their stage. This is essential in determining surgical management, tracking response to therapy and prognosis (Plöckinge, 2005).

TREATMENT OF THE PRIMARY NEUROENDOCRINE TUMORS OF THE THYMUS

Primary neuroendocrine tumors of the thymus are rare yet very aggressive tumors, which grow relatively slowly. In almost 80% of the cases, they are malignant. NETTs very often infiltrate adjacent tissues. Local recurrence may occur many years later. They are more frequently diagnosed in men in the fourth and fifth decade of life. Nearly half of the cases are associated with endocrinology, such as Cushing's syndrome or acromegaly (Pier Luigi Filosso, 2017).

Completeness of resection is believed to be the strongest prognostic factor in the prognosis of this disease (Filosso, 2014). It has been found that patients in early stage of NETT survived longer and developed recurrences less frequently (Filosso, 2015). Furthermore, tumor size and metastatic development are also important in prognosis. According to previous studies, tumors with associated endocrinopathies also act more aggressively than tumors without them (Rabinowitcz, 2006). It was observed that patients with NETT and Cushing's syndrome or MEN-1 syndrome had a higher mortality rate than those without paraneoplastic syndromes (Wick, 1980).

Patients with NETT should be routinely referred to experienced centers and multidisciplinary facilities. For NETT, surgery to reduce the tumor mass is recommended to alleviate clinical symptoms resulting from the secretory activity of the tumor. These tumors respond poorly to radiotherapy. The treatment of choice is surgery because almost 80% of thymic NETT cases behave malignantly (Moran, 2000). Complete resection of the tumor along with the involved mediastinal structures should always be sought. The preferred approach for NETT resection is through a median sternotomy. For advanced tumors, anterior thoracotomy, lateral thoracotomy, posterior-lateral thoracotomy, alone or in combination with sternotomy (combined access) can be used, which provide good exposure of the entire mediastinum and pleural space (Huang, 2008). Despite this, these tumors can often infiltrate adjacent structures and cause distant metastasis and recurrence, making their complete resection sometimes difficult and their prognosis poor (Pier Luigi Filosso, 2017).

NETT recurrences can be local, occurring in the anterior mediastinum, regional, present within the chest, or distant, occurring outside the chest or in the case of intrapleural nodules. An aggressive surgical approach if complete resection of the recurrence is possible and postoperative RT is thought to be effective in recurrent NETTS and to increase survival. (Sakuragi, 2002). For advanced NETT, induction chemotherapy (or CT + RT) has been used to reduce tumor size, increasing the likelihood of R0 resection (radical resection), although studies do not clearly define the effect of such a process. (Pier Luigi Filosso, 2017). Postoperative radiotherapy (or CT + RT) is also used for incomplete resections. Based on the reported cases, the medium-term survival in patients with NETT was quite good, especially in the case of complete surgical resection.

When surgical treatment is not possible, pharmacotherapy with somatostatin analogues, a hormone that inhibits secretory and cell proliferative processes, can be used. Somatostatin analogues are very well tolerated and usually relieve discomfort resulting from the

secretory function of tumors (Dasari, 2017; Halperin, 2017; Davar, 2017).

A form of molecularly targeted therapy, peptide receptor radionuclide therapy (PRRT), appears to be very effective in the systemic treatment of metastatic thymic neuroendocrine tumors. PRRT is performed using a somatostatin analogue similar to octreotide, absorbed by the tumor, coupled to a radionuclide usually 177 lutetium and 90Itr emitting beta radiation that kills the tumor cells (Pier Luigi Filosso, 2017).

In order to reduce the tumor mass of metastases, thermoablation techniques are used, i.e. destroying cells with high temperatures obtained by laser or radiofrequency. In some patients with NET tumors, characterized by a high capacity for rapid cell division, classical chemotherapy is also used (Dasari, 2017; Halperin, 2017; Davar, 2017).

In MEN1 patients in whom NETT is a major cause of death, several prophylactic thymic resections at the time of parathyroidectomy using the same surgical access are suggested to reduce the risk of NETT (Teh,1998) (Trump, 1996).

As there is a high risk of recurrence or development of distant metastases in patients with NETT, close and lifelong follow-up of the patient is required. It is suggested to perform a chest CT every 6 months for the first 3 years (Pier Luigi Filosso, 2017).

THE IMPORTANCE OF EMPERIPOLESIS IN THE CONTEXT OF DEVELOPING FUTURE DIAGNOSTIC AND TREATMENT METHODS

In terms of diagnostics, it seems appropriate to conduct extensive research on a large population of neoplastic cells of neuroendocrine origin in terms of the occurrence of the phenomenon of emperipolesis. Based on the various studies and descriptions of clinical cases cited earlier, we conclude that there is a likelihood of a significant correlation between the number of cells in emperipolesis and a specific type of cancer. Furthermore, it is noteworthy that the proportions between different types of cells can serve as an indicator of a given tumor development and progression. It may be important to observe cells in the state of emperipolesis in a microscopic image and find the relationship between the occurrence of a specific image of cells and frequent detection of a specific tumor.

The use of lymphocytes in targeted therapy is very promising (Goswami, 2019). T lymphocytes tend to bind to antigens of cancer cells, which may be crucial for introducing therapeutic substances into cancerous cells, not into healthy ones. Targeted therapy can then only cover diseased cells, leaving healthy cells intact.

In biotechnology, great opportunities are attributed to the importance of liposomes as potential carriers of anti-cancer drugs (Temidayo, 2018). If the process of emperipolesis were to be explored even more and we would get an answer to the question of what induces emperipolesis, then one can try to construct a liposome that would resemble a lymphocyte externally, induce emperipolesis and thus deliver the drug to the inside of cancerous cells. Such a solution could be used locally or systemically if there is a risk of neoplastic metastases, since the outer surface of the liposome would have specific receptors targeting specific tumor epitopes distributed throughout the body.

A slightly different method could be to modify T lymphocytes by introducing specific drugs inside them and then using it in molecularly targeted therapy. This would save time and the biotechnological construction of the receptors would not be necessary, as we would use the receptors already present on the T lymphocytes.

Moreover, radioisotope therapy can be used in the treatment of neuroendocrine tumors of the thymus (Iskanderani, 2018). It is a molecularly targeted therapy in which a specially selected peptide, having the property of attaching to a cancer cell, is combined with a small amount of radioactive material to form together a drug (radiopharmaceutical) called a radiopeptide (Kolasińska-Ćwikła, 2018). After the injection into the patient's bloodstream, radiopeptide travels with the blood, reaches the tumor and attaches to the cancer cells, providing them directly with a therapeutic dose of radioisotopic radiation. The tumor absorbs both the drug and the radionuclide, and the emitted beta radiation particles kill cancer cells. The most effective radionuclides currently used are 177Lutet and 90Yttr.

SHORT CONCLUSION

Emperipolesis is a rare biological phenomenon, in which a cell penetrates another living cell. Emperipolesis is often described in relation to the thymus gland, however the precise mechanisms underlying this process are still elusive. In this publication we have reviewed previous findings and determined the importance of emperipolesis in tumors formation and progression.

Lymphatic emperipolesis may occur in thymic epithelia-reticular cells. It is crucial to clarify the relationship between the presence of a particular cell image during emperipolesis and the detection of a particular type of cancer. Among available diagnosing techniques, imprint smear is an effective and quick method for detecting emperipolesis.

Thymic neuroendocrine tumors (NETTs) are rare tumors with high aggressiveness that present many non-specific symptoms. Diagnostic techniques that are most commonly used in neuroendocrine tumors assessment are ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). The treatment of choice is surgery. The completeness of resection is the strongest prognostic factor, nevertheless PRRT appears to be very effective during therapy. Targeted therapy can cover only diseased cells, leaving healthy cells intact. The use of modified T lymphocytes in targeted therapy by introducing specific drugs inside them is an emerging and very promising method in treating cancer.

There is still a lot to uncover regarding emperipolesis, especially in terms of using this phenomenon in the therapy and treatment of cancer. An interesting approach would be to construct the liposome that delivers the drug to the inside of cancerous cells. The combination of the well-known treatment methods with not yet fully understood em-peripolesis, may open up new possibilities especially in the treatment of neuroendo-crine tumors of thymus.

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