Differential Diagnosis in Esophageal Cancer

Review on literature

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Esophageal cancer represents a neoplasm that is thought to have both an increased incidence and prevalence in the following years. Although much progress has been made in the detection and the early treatment of esophageal cancer, the prognosis is still limited, and mortality remains very high. The most common histological types of esophageal cancer are squamous cell carcinoma, and, respectively, adenocarcinoma. Lately, there has been an accelerated increase in the incidence of adenocarcinoma, in the context of increased prevalence of gastro-esophageal reflux disease and obesity, but also of the current alimentary diet, especially in developed countries. The esophagus has its anatomical features. Moreover, it is located topographicallyin a complex cervico-thoraco-abdominal area, unique for a viscus. From the clinical point of view, the onset of symptoms of esophageal cancer is insidious. For these reasons, special attention should be pain in the early detection and differentiation of this neoplasm from other pathologies. These pathologies are very varied and may comprise other esophageal diseases, neighborhood pathologies such as cervical, thoracic, abdominal, systemic pathologies (immunologic, infectious) or other pathologies such as the oro-maxillo-facial, oculo-orbital, vascular, muscular, and cutaneous ones.

Keywords: esophagus, cancer, differential diagnosis

Esophageal cancer is a severe neoplasm, with increased morbidity and mortality and limited prognosis. Located on the eighth place in the global incidence scale of neoplasms, it is the second esophageal pathology in terms of frequency after the reflux disease [1-3]. In the following years, by 2025, an increase of esophageal cancer prevalence by 140% is suspected, unlike many other types of cancer, whose incidence is expected to decrease [4,5]. Although much progress has been made in the diagnosis and treatment of esophageal cancer, the survival rate of 5 yearshas not significantly changed, varying between 15% and 20% [6].

The incidence of espohageal cancer varies according to the geographical area and correlates with exposure to different risk factors [3]. An increased risk of esophageal cancer occurrence was noticed with age, especially in the sixth and seventh decades. Male patients are three times more frequently affected [1,2]. Other risk factors involved in carcinogenesis are: genetic susceptibility, diet and nutrition, tobacco and alcohol, precancerous states, human papilloma virus infections [1].

The epidemiology of esophageal cancer has dramatically changed over the past 40 years, especially in developed countries. If squamous cell carcinoma was predominant in the past, adenocarcinoma is more common nowadays, due to the increased prevalence of gastro-esophageal reflux disease and obesity [5,7,8]. The two histological types of the most commonly encountered esophageal cancer are adenocarcinoma and squamous cell sarcoma. Only 1-2% of esophageal cancers are sarcomas, lymphomas, melanomas, carcinoids and small cell carcinomas [9-12]. New specific risk factors have been discovered for each of the two major histological types of esophageal cancer. Responsible for the occurrence of squamous carcinoma seem to be risk factors such as: alcohol consumption, tobacco, certain salty vegetables and canned fish [13-16]. On the other hand, gastro-esophageal reflux disease, respectively Barrett's esophagus and obesity seem to be related to the occurrence of esophageal adenocarcinoma [8,17,18]. The results of some recent research should be noted, which revealed histopathological changes specific to esophageal adenocarcinomas represented by local neoangiogenesis [19].

Esophageal cancer has an insidious and apparently painless onset. Superficial lesions are completely asymptomatic and discovered accidentally during an endoscopic examination. Symptomatology has dysphagia as a central element, which occurs in 90% of patients and it can be accompanied by odynophagia, anorexia, sialorrhea, regurgitation and weight loss. In the event of an unfavourable development of the disease,along with the loco-regional neoplastic extension, but also distance, many other signs and symptoms may also appear: hoarseness, irritable coughing, whooping cough at deglutition, mediothoracic pain, stridor, cervical and supraclavicular adenopathies, Claude-Bernard-Horner syndrome, jaundice, bone pain, neurological deficits and even upper digestive hemorrhages [1,2]. Differential diagnosis of dysphagia include ENT pathology [20,21].

Due to the local topography of the esophagus and the insidious symptoms of esophageal cancer, we consider that the presentation of the differential diagnosis of esophageal cancer with other esophageal or neighbouring pathologies is of major importance [22]. Although we currently have numerous modern technical means of diagnosis, some authors consider that the differential diagnosis can only be made based on the symptoms andthe correct interpretation of radiological investigations, before the use of endoscopy and the result of the pathological examination of the biopsy fragments [23].

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First of all, esophageal neoplasms must be distinguished from other esophageal pathologies. The most common esophageal pathology which is being discussed is the gastro-esophageal reflux disease. Differentiation is done by using pH-metry measured over a 24-hour interval [1]. If gastro-esophageal reflux disease is neglected, the most common complication which occurs as a long-term evolution is the occurrence of Barrett's esophagus. In these situations, upper digestive endoscopy with biopsy is used to differentiate Barrett's esophagus from a possible benign intestinal metaplasia, dysplasia or even invasive esophageal cancer [24]. Early esophageal squamous carcinoma may simulate reflux esophagitis, another possible complication of the gastro-esophageal reflux disease and, therefore the differential diagnosis between these two conditions is very important for this reason [25].

Benign esophageal masses typically have a long history of retrosternal scalding pain accompanied by slow progressive dysphagia, and the differentiation from esophageal cancer is done by performing eso-gastro-duodenoscopy, which will reveal the benign etiological stricture [24]. Studying the clinical, imaging and histological aspects of some diffuse esophageal leiomyomatosis made it possible to differentiate this benign tumor from a possible leiomyosarcoma [26]. Another benign esophageal pathology, rarely seen, pseudo-epitheliomatous hyperplasia, should be taken into account for the differential diagnosis of esophageal neoplasms [27].

Other esophageal tumors are similar to esophageal cancer. The studies have described the presence of eso-gastric masses, suspected of being gastro-intestinal stroma tumors(GISTs), due to similar characteristics and which appeared to have the cancerous aspectof gastro-esophageal junction during the pathological examination [28-30]. Another study shows that an esophageal mass suspicious of being esophageal junction cancer has proven to be esophageal Paget's disease (the fifth case described in the literature) associated with esophageal cancer (the first association of the kind in the literature) [31].

Hiatal hernias have been a very common pathology lately. Microscopic research has revealed the loss of elasticity and the decrease in the functionality of the diaphragm muscle [32]. It has been noticed that in some situations, respectively in the case of elderly patients, hiatal gliding hernias may mimic the existence of esophageal cancer [33]. Approximately 10% of hiatal hernia patients experienced concomitant esophageal cancer, which makes the differential diagnosis between the two esophageal pathologies extremely difficult [34].

Several studies have highlighted similarities between esophageal tuberculosis and esophageal cancer. A paper presents the case of a patient suspected of the presence of a tumor mass in the middle thoracic esophagus, although no bacteriological changes were noticed, and the endoscopic ultrasound and the histopathological examination suspected the presence of tuberculous esophagitis. The antituberculous treatment was begun, with the gradual improvement of the symptoms and only after 8 weeks of evolution it was possible to isolate tuberculous bacilli from the sputum [35]. Other authors also suggest that esophageal tuberculosis can be similar to esophageal cancer, being difficult to differentiate [36-39].

Other different esophageal pathologies are similar to esophageal cancer: peptic strictures [40], Zenker diverticulum ulcers [41], chronic esophageal perforation with peri-esophageal abscess [42], candidiatic esophagitis [43,44]. Patients with achalasia have a long history of regurgitations, unaccompanied by burning pain and therefore the presence of esophageal cancer may be clinically suspected. In this case, the eso-gastroduodenal barium swallow is used, which will reveal a typical *bird's beak* filling defect [24]. Intramural esophageal hematomas, rare esophageal lesions, gastroesophageal varices, may resemble hemorrhagic esophageal cancer, but the use of computed tompgraphy (CT) with contrast medium will help in making the proper diagnosis [45,46]. And, last but not least, a study based on a group of ten thousand patients presented the differential diagnosis between the presence of esophageal ectopic sebaceous glands (which occur in 0.05% of asymptomatic patients) and esophageal cancer [47].

Dysphagia, an important symptom in the clinical picture of esophageal cancer may have many other different causes. One of these are primary motor esophageal disorders (aclasia of the cardia, diffuse esophageal spasm, hypertensive lower esophageal sphincter), which will differentiate from a possible esophageal cancer by the use of esophageal manometry [1]. Other pathologies which lead to oro-pharyngeal dysphagia (cerebro-vascular accidents, cricopharyngeal achalasia, myasthenia gravis, etc.) will be diagnosed by means of video-fluoroscopy in order to monitor the crico-pharyngeal phase of deglutition [1]. Other etiologies are vascular disorderscomprising vascular malformations (mediastinal ganglionic metastases, tumoral penetrations),revealed by cervical and thoracic magnetic resonance imaging (MRI) with vascular reconstruction [1]. Tuberculous mediastinal lymphadenitis is a very rare pathology. A study presents two cases of dysphagia due to tuberculous mediastinal lymphadenitis which, from a radiologic and endoscopic point of view appeared to be esophageal neoplasms [48]. Different neurological causes may be involved in the occurrence of dysphagia; the neurological pathologies being identified by computed tomographies or cerebral magnetic resonance imaging [1]. Benign peripheral nervous tumors may lead to dysphagia. The first case of esophageal perineurinoma accompanied by dysphagia is cited [49]. Differentiation from myasthenia gravis is based on electromyogram performance, on the antibodies against acetylcholine receptor and those against MuSK protein [1]. Dysphagia of otorhinolaryngologic origin, due to the existence of some expansive processes or extrinsic compressions requires an ENT examination in order to evaluate the upper airway passages [1]. There are also other causes of dysphagia. A study presents the case of a known breast cancer patient and who presents to the hospital for dysphagia after 11 years from the diagnosis. The presence of a presumptive tumor originating in the esophagus was suspected, but the result of the histopathological examination confirmed the presence of solitary esophageal metastasis of relapsed breast cancer [50].

Various ocular pathologies, apparently without a causal relationship to esophageal pathology have been reported in the literature as sites for metastases of esophageal cancer. A study presents the metastatic damage of the orbit 6 months after a patient was diagnosed with esophageal adenocarcinoma [51]. Another study revealed the presence of metastasis in the extrinsic eyeball muscles, secondary to an eso-gastric junction adenocarcinoma in a patient with diplopia and decreased visual acuity [52]. With strict reference to the eyeball, the authors of a study present the case of a patient diagnosed with esophageal squamous carcinoma metastasis in the left iris, which determined ocular pain and increased

intraocular pressure [53]. Choroidal metastases are the most common intraocular malignant tumors. In this regard, a study presents the first case of bilateral choroidal metastasis following an esophageal manignant melanoma [54]. A metastatic case of esophageal cancer was also decribed in the retina [55].

Esophageal cancer may be masked by the presence of various pathologies in the oro-maxillo-facial and cervical area. A patient with dysphagia accompanied by increased dimension of the right cervical region, chills and fever was diagnosed with Lemierre Syndrome (thrombophlebitis of the inner jugular vein, consequence of a peri-tonsillar abscess), caused by a Streptococcus anginosus. Since the initial symptom was intense dysphagia, the evacuation of the abscess was performed at first. Subsequently, upper digestive endoscopy was performed and esophageal cancer was discovered [56]. Other authors present the first case of proximal esophageal adenocarcinoma located in the thyroid in a young patient without any history of neoplasms [57]. Another study presents a metastatic case of esophageal cancer in the mandible, simulating edontogenic infection or benign mandibular mass formation [58].

Thoracic disorders represent another category of pathologies that need to be differentiated from esophageal cancer. In this sense, a thoracic pain which may be attributed tothe clinical picture of an esophageal cancer may be, in fact, the cardiac cause and the confirmation of the cardiac cause is done by electrocardiogram performance, echo-cardiography and cardiac examination [1]. A study presents the case of a patient with cardiac metastasis following esophageal squamous carcinoma, who presented himself to hospital simulating acute myocardial infarction. Based on the histopathological examination, the disgnosis of certainty was made [59]. Other authors also present left ventricular metastasis of esophageal cancer simulating myocardial infarction [60]. On the other hand, the other major componentof intrathoracic pathology, i.e. respiratory pathology, such as mediastinitis, pleurisy, dyspnea, atypical pneumonias must be taken into account when esophageal cancer is suspected [61]. Stridor represents a very rare cause of visits to the hospital in case of esophageal cancer patients. However, the authors of a study have described the case of a patient diagnosed with esophageal cancer and who presented to the hospital for stridor 7 years following diagnosis and, respectively, treatment. The investigations revealed the relapse of esophageal cancer, which determined the occlusion of the trachea and secondary respiratory failure [62]. The authors of a study describe the first case of ectopic retrotracheal thymoma with clinical and imaging characteristics that mimicked the existence of an esophageal tumor [63].

Abdominal disorders participate in the differential diagnosis of esophageal cancer. Among inflammatory intestinal disorders, Crohn's disease was noticed to mask the evolution of esophageal carcinoma [64]. The first case of metastasis following esophageal adenocarcinoma in the small intestine was described, which determined the occurrence of subocclusive syndrome due to ileocecal invasion [65]. Metastases were also identified in the spleen, secondary to esophageal squamous carcinoma, with only five such cases presented in the literature. These splenic formations are similar to primary splenic lymphomas from a macroscopic and radiologic point of view [66,67].

Anoher category of diseases that must be distinguished from esophageal cancer are immunological diseases. Studies have revealed an association between cancer in general and scleroderma. Dysphagia and motility disorders of the scleroderma are symptoms that can delay the diagnosis of gastro-esophageal cancer [68]. The differentiation from scleroderma is based on the evaluation of anti-topoisomerase antibodies (ATAs) (anti-scl70) and anticentromere antibodies (ACAs) [1]. Dysphagia could rarely appear also in another vasculitis [69,70].

The suspicion related to the presence of an infectious disease requires an infectious disease specialist consultation. Pulmonary tuberculosis and associated mediastinal lymphadenopathy may cause dysphagia, which is why tuberculin intradermal reaction is used and the objectivation of Koch bacillusfrom sputum associated with imaging methods [1]. Actinomycosis, an opportunistic infection, may lead to the occurrence of dysphagia and weight loss. Cases in which actinomycosis may co-exist with esophageal cancer are described in patients with dysphagia and for this reason it is necessary to perform upper digestive endoscopy and a histopathological examination in order to differentiate between the two pathologies [71,72].

Skin lesions are also considered for the differential diagnosis of esophageal cancer. Only five cases of cutaneous metastases are described in the literature, secondary to esophageal adenocarcinoma, which rarely metastasizes to the skin. The predisposition of these masses is on the scalp and they appear as painful cutaneous nodules, asymptomatic at first [73-75]. The presence of cutaneous metastasis was also described on the face as a small mobile painless nodule [76]. A cutaneous metastasis was also presented at the tip of the nose, which was the first sign of an extended esophageal squamous carcinoma [77]. Other authors have presented the case of a patient who developed melanocytic diffuse macules and papules which have proven paraneoplastic cutaneous manifestations of an advanced distal esophageal carcinoma [78,79]. Tylosis, palmar and plantar hyperkeratosis, is characterized by focal thickening of the skin of hands and feet. Although it is a hereditary dermatological pathology, an association between tylosis and esophageal squamous carcinoma was noticed, especially in advanced ages [80].

Striated muscles are a very rare site for metastasis. However, studies have revealed metastases in skeletal muscles (from the thigh, respectively lumbar spine) secondary to espohageal cancers [81-83]. The articular system is not deprived of the presence of metastases. The knee joint was the seat of an esophageal adenocarcinoma, the first case of malignancy in the synovial joint of the knee being described. Although rare, malignant synovitides represent an important differential diagnosis in patients with unexplainable monoarthritides [84,85].

Acute arterial embolisms due to malignant tumors are rare. But a study presents the case of a patient who was diagnosed with acute arterial occlusion in his left lower limb. Following embolectomy, it was found that the embolus originated in the esophageal squamous carcinoma [86]. Pulmonary thombembolism is a consequence of deep venous thrombosis, thus, anticoagulant profilactic therapy is very important, knowing the procoagulant neoplastic state [87,88].

Other atypical locations of metastases from esophageal neoplasms were described in the literature. The first metastasis in the interventricular choroid plexus was described at a cerebral level [89]. The authors of a study present the case of a patient, known with history of esophageal adenocarcinoma and who developed an inflammatory mass with overlying progressive

integumentary erythema at the right breast. Immunohistochemistry differentiated esophageal adenocarcinoma metastasis from the suspicion of an inflammatory breast carcinoma [90]. As for the urinary system, esophageal adenocarcinoma metastases were also noticed in the urinary bladder, and respectively in the prostate (the first case cited in the literature) [91,92].

Retroperitoneal tumors, with or without mediastinal extension, should also be differentiated from esofagean cancer [93].

The bioethical and psihological aspects of comunicating the diagnostic of cancer, especially with poor prognosis, to patients or their families are very complex [94-96].

Conclusions

Esophageal cancer is a relatively common neoplasm, with an increased incidence lately, with limited prognosis and sustained mortality despite the progress made in the surgical and oncological treatment of this condition.Due to the insidious symptoms of esophageal cancer, especially in its early stages, but also due to the complexity of the topographical regions corresponding to the esophagus, it is necessary to have a good knowledge of the differential diagnosis between esophageal cancer and the exhaustive esophageal pathology, periesophageal, but also of the entire body so that the appropriate therapeutic decision be made as early as possible.

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