Occult neoplasm: a medical service experience

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Abstract

Cancer of unknown origin has a variable presentation making always difficult its evaluation. Few papers have been published concerning this subject. The AA made a two year retrospective study of all patients admitted to the Medical Service of Faro District Hospital.

Cancer was diagnosed in 469 patients, with a diagnosis of cancer of unknown origin in 34. The authors evaluated the following: gender and age distribution, clinical and laboratory data on admission, diagnostic workup, sites of metastization, cytology or histology of the tumorous, clinical evolution and therapy.

Cancer of unknown origin accounted for 6.8% of the total number of patients in whom neoplastic diseases were diagnosed. The average age was 72 years with a male predominance. The clinical and laboratory data on admission had no relevance to the final diagnosis. Ultrasonography and computerized axial tomography were the exams most requested.

The liver was the most frequent site for metastases, and carcinoma was the most frequent diagnosis made through cytology or histology. The average survival is 81.9 days. Only 4 patients started curative chemotherapy and three of them are still in remission after a follow-up of more than two years.

Keywords: cancer of unknown origin.

Introduction

A diagnosis of occult neoplasm (ON) is considered when:[1]

• Cytological or histological findings prove the existence of neoplasms.

• his result is not compatible with a primary neoplasm of that organ or tissue.

• The primary location of the neoplasm is not evident, despite clinical history, physical examination, and complementary diagnostic exams appropriate for each case.

Despite the scientific and technological advances, this is still a relatively common clinical entity, accounting for 5 to 10% of patients with neoplasm.[2]

The incidence of ON is rare before forty years of age and increases with age, with an average age at diagnosis of sixty years.[1,3]

The prognosis is generally poor, with an average survival of three to four months. Less than 25% of patients survive for one year and less than 10% survive for five years.[2,5] This prognosis is, however, more favorable in the subgroups of patients referred to in the tables below.

As regards clinical presentation, about fifty percent of patients with ON have multiple metastases. The remainder of the patients presents single metastases, occurring most often in the liver (25%), bones (22%), lungs (20%), adenopathies (15%), pleura (10%) and brain (5%).[3]

As regards the cytological and histological findings, about 50 to 55% of patients have metastatic adenocarcinomas, about 30% have undifferentiated or poorly differentiated carcinomas, and the remaining 20% have a variety of types of tumors, including squamous cell tumors, endocrine tumors, sarcomas, lymphomas, stem cell tumors, melanomas, and non-classifiable tumors.[3] It should be noted here, however, that there is some disparity in relation to the percentages reported in the various studies published.

The extreme heterogeneity of the clinical presentations, histological findings, and natural histories of ON makes systematic evaluation of this disease very difficult.[2] However, despite these difficulties, some standards are now accepted by most authors:

1. Highly detailed radiological studies can reveal the extent of the metastatic disease, but do not necessarily detect the primary location.

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TABLE I

Occult neoplasm

Neoplasms with more than 50% response	Curable neoplasms
Head and Neck	Lymphoma
Thyroid gland	Stem cell tumor
Small cell tumor	
Breast	
Ovary	
Endometrium	
Prostate	

2. The tumor markers currently available have proven to be unsatisfactory in establishing, with precision, the origin of the metastases in a patient with ON, although in certain specific cases they seem to have complementary value for the evaluation of these patients.[3,4,7]
3. An exhaustive search for the primary site, while theoretically offering several advantages (specific treatment, prevention of local complications, improved prognosis), is, in practice, of little interest because:
• It prolongs the hospital stay excessively;
• It is extremely costly;
• It does not contribute to the improvement of the patient's clinical condition or prognosis.

Thus, the clinical diagnosis of this type of patient should be made using simple diagnostic means that allow us, when faced with a patient with occult neoplasm, to identify the following (*Tables 1 and 2*):
• Primary tumors for which non-palliative treatment is available;
• Groups of patients for whom, even without identification of the primary tumor, there are therapeutic regimens to improve survival.

Hence, the critical step for a precise diagnosis of potentially curable primary tumors is a histopathological exam of the malignant tissue, which should be more and more often routinely supported by an immunocytochemical evaluation and, in selected cases, electron microscopy and genetic analysis.[4] Moreover, improvements in the treatment options available for metastatic disease with pulmonary and gastrointestinal (including the pancreas) origins are necessary, given that most patients who do not respond to therapy seem to have primary tumors located in these organs.[5]

TABLE II

Occult neoplasm: Patients with better prognoses

CLINICAL CRITERIA
- Young, non-smoker, single metastasis
- Young, cervical lymph node adenopathies, squamous cell histology
- Female, axillary lymph node adenopathies, adenocarcinoma histology
- Female, malignant ascites or peritoneal carcinomatosis, serous/papillary carcinoma histology

HISTOLOGICAL CRITERIA
- Neuroendocrine tumors
- Stem cell tumors
- Small cell tumors

HISTOLOGICAL AND CLINICAL CRITERIA
- Less than 50 years old, mediastinal or retroperitoneal mass, poorly differentiated carcinoma/adenocarcinoma histology

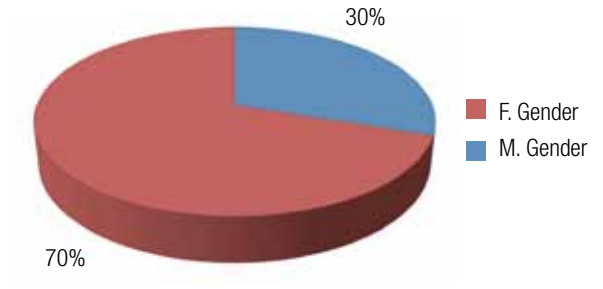
Material and methods

The clinical records of thirty-six patients with diagnoses of ON were studied. Of these patients, two were excluded from our study because the primary tumors (lung tumor) were identified during the autopsy. The following parameters were analyzed: distribution by gender and age group, clinical manifestations and initial analytical changes, location of metastasis, cytology/histology, complementary exams, and clinical and therapeutic evolution.

Results

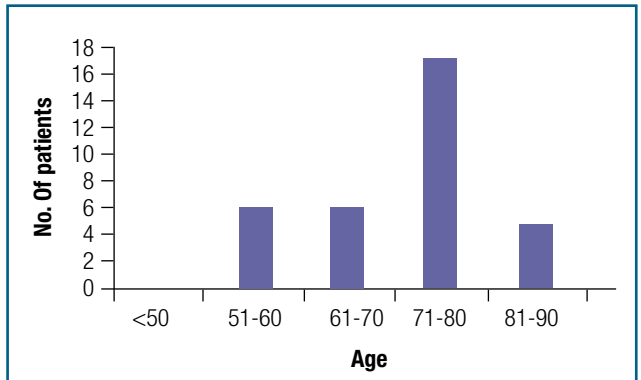
Patients with ON accounted for 6.8% of the total number of all cancer patients. Of these, there was a predominance of male over female patients (*Fig. 1*). The average age of the patients was seventy-two, with distribution by age as shown in *Fig. 2*.

Regarding the initial clinical condition (*Fig. 3*), in more than fifty percent of cases (twenty-two patients) clinical manifestations were of short duration (on average, two to three months) and non-specific: anorexia, asthenia, and weight loss. Of these twenty-two patients, fifteen (44%) presented concomitant signs and/or symptoms related to the site of metastasis; in particular, increase in abdominal volume (malignant ascites), changes in behavior, headaches, hemiparesis (cerebral metastasis), bone pain, pathological fracture (bone metastasis), changes in vision (retinal or cere-



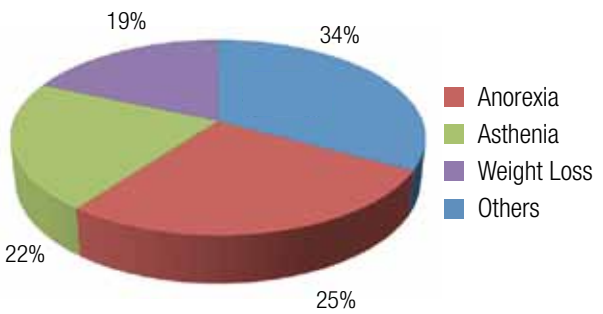
Distribution by gender.

FIG. 1



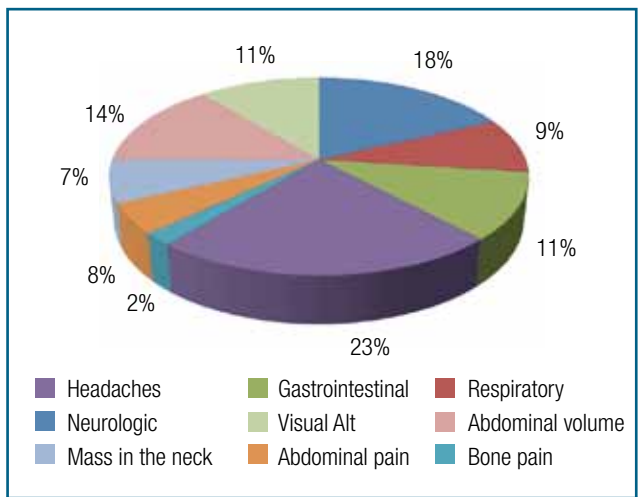
Occult neoplasm.

FIG. 2



Signs and symptoms.

FIG. 3A



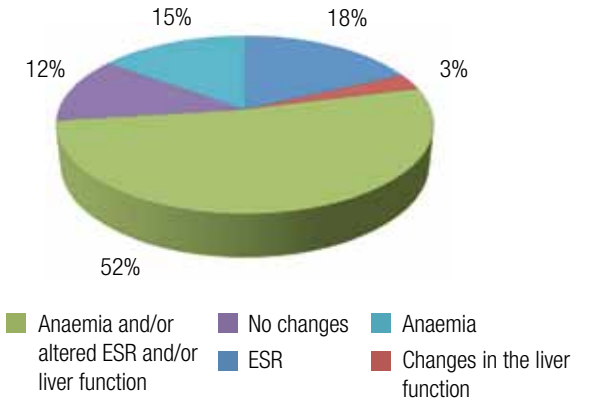
Signs and symptoms (others).

FIG. 3B

bral metastasis), abdominal pain (liver metastasis), mass in the neck (lymph node metastasis). Eight patients (23.5%) showed only signs and/or symptoms related to the site of metastasis, which in these cases were cerebral, bone, or lymph node metastases. Nine patients had complaints unrelated to the site of metastasis several months into the evolution of the disease, in particular, gastrointestinal complaints (chronic constipation and dyspepsia).

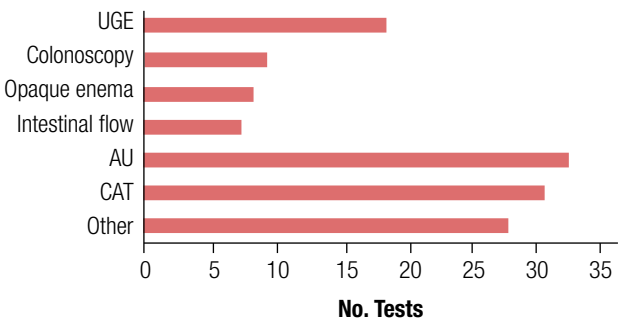
Minor, non-specific analytical changes were observed (*Fig. 4*). Seventeen patients (50%) had a variable combination of anemia and/or elevated ESR and/or abnormalities in the liver function tests and 4 patients (20.5%) showed no analytical changes. The type of anemia was normochromic-normocytic, with an average hemoglobin count of 11 g/dL. Average ESR values were between 25 and 50. Liver function tests showed no predominant pattern of cholestasis or hepatocellular lesions. Two patients had microcytic anemia with ESR values of 100: one man, with metastatic cervical lymph node adenopathies of squamous cell carcinoma, whose radiological exams pointed to a likely origin in the cavum and one woman, with peritoneal carcinomatosis of undifferentiated carcinoma, whose tumor markers pointed to a probable ovarian tumor.

The locations of the metastases are detailed in *Fig. 5*. It should be noted that thirteen patients (38%) had a single site of metastasis, most often in the liver (five patients – 38.5%). Other locations of single metastasis were the cervical lymph nodes (four patients), the brain (three patients), and the bones (one patient).



Analytical Changes.

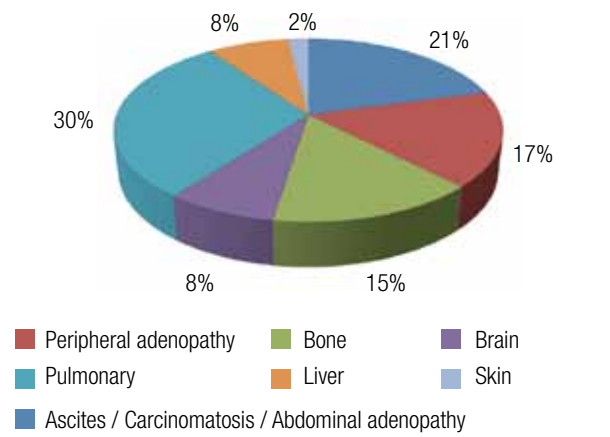
FIG. 4



UGE, Upper gastrointestinal endoscopy; AU, Abdominal ultrasound

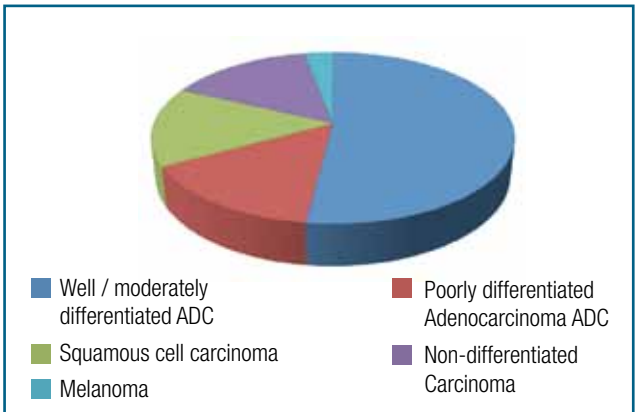
Additional tests.

FIG. 6



Metastasis site.

FIG. 5



Cytological / histological diagnoses.

FIG. 7

The most frequently requested complementary exams were abdominal ultrasound (thirty-two patients) and computerized axial tomography (thirty patients). (*Fig. 6*). The category "Others" includes thyroid ultrasound, laryngoscopy, bronchoscopy, bronchial wash cytology, pleural biopsy, pelvic, prostate, and testicular echograms, biopsy of the endometrium, mammogram, bone scintigraphy, nuclear magnetic resonance, and tumor marker tests.

The cytological/histological diagnoses are documented in *Fig. 7*. The most frequently used diagnostic techniques were liver biopsy and aspiration cytology/ lymph node biopsy.

In relation to the patients' clinical evolution, the following are highlighted:

- Average survival was 81.9 days;
- Fifty percent of the patients died during the hospitalization in which the diagnosis was made;
- Fourteen patients had autopsies that failed to locate the primary tumor.

Of the seventeen patients who survived, only four began non-palliative treatment:

- One man with metastatic cervical adenopathies of squamous cell carcinoma underwent surgery followed by localized radiotherapy;

• Three women with liver/peritoneal metastases of moderately differentiated adenocarcinoma, two of whom had elevated CA 125 levels, began chemotherapy with cyclophosphamide and carboplatin.

All of the patients who began a program comprised only of palliative therapy died. Of the other four patients, one of the women died after seven months of treatment, while the other three were still in remission after more than two years of evolution.

Discussion

Studies published about ON indicate that this entity represents five to ten percent of the total number of neoplastic patients. This variance in percentage of incidence depends essentially on the depth of each study and the population included.

There is some disagreement concerning the distribution by gender and age. Some studies report a prevalence of male patients, while others report no difference between genders. Moreover, the average age reported also varies, although always below sixty years of age. In our study, the average patient age was slightly higher. This result is probably distorted by the small number of patients included in the study, which makes it easy for the local characteristics of a population to influence this type of index.

Few studies have been conducted in relation to clinical profiles and initial analytical changes. There is, however, a general consensus that a patient with ON typically develops clinical manifestations related to the location of the metastasis and not to the location of the primary tumor.[2] According to a study by Mayordomo et al[6], clinical manifestations are most commonly related to the deterioration of the patient's general condition (73%) and analytical changes, while common, are non-specific, as occurred in our case.

As to the sites of metastasis documented, there was a higher percentage of patients with liver metastases in the other studies compared to the data reported in our work.[1,3] However, the relative proportions between the different types of clinical presentation remained consistent. Also, in relation to the sites of single metastasis, several discrepancies were noted relative to the data in the literature,[3] in particular, a higher proportion of single metastases in adenopathies and the brain. The same applies to the percentages of the different types of carcinomas identified through cytological/histological diagnosis.[2,6] We believe that all of these variances in percentages in our results are due to the small number of patients included in our study. It is important to point out that even in studies with larger numbers of patients, there are variances in the percentages reported for each of the parameters, emphasizing the difficulty, mentioned earlier, in the systematized study of patients with ON and the variances that exist between different population groups.

In our analysis of the data from the requested complementary diagnostic exams, and besides making our critical evaluation of the results, we must not forget the difficulty that still exists today in systematizing the evaluation of a patient with ON, a difficulty that perhaps was not well expressed in the introduction of our study, where we have tried to be as systematized as possible. Thus, for example, it is debatable as to whether or not the initial evaluation of these patients ought to include an abdomino-pelvic CAT scan. This diagnostic technique enables the identification of around thirty to thirty-five percent of primary tumors, usually in the pancreas, kidneys, liver/biliary tract, and ovaries.[5,7,8] However, as is usually the case, only the ovarian tumors are sometimes treatable. The same applies to research of a primary gastrointestinal tumor. Some authors argue that an upper digestive tract endoscopy/colonoscopy should be indicated in all patients with adenocarcinoma and abdominal complaints, ascites, liver metastasis, or microcytic anemia.[3] Thus, endoscopic exams of the gastrointestinal tract are the tests most frequently requested for patients with ON, even though there is little evidence that the possible detection and even the resection of asymptomatic primary gastrointestinal tumors and metastases, significantly improves the patient's survival time or quality of life.[2,3,5]

In regard of the average survival time of the patients and clinical evolution, our results are in accordance with other studies on the subject – poor prognosis and few treatment options, with the exception of specific groups of patients upon whom, as we pointed out in the introduction of this paper, we should focus our diagnostic evaluation. ■

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