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Short Communication

The Still Elusive Cancer of Unknown Primary Site (CUP)

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First as a medical student and second as an early Oncologist practitioner in anatomopathological athenaeums, I faced with similar CUPs in 2 patients.

In the first one, Dr Barcat, a brilliant pathologist, cut the thyroid in nearly "100 pieces" and found the primary tumor in this gland.

In the second one, my Clinical Cancer diagnoses failed: in the deceased patient the thyroid was the primary tumor organ site (it is to mention early here, that in some CUPs, sometimes the metastatic phenotype histology is quite-difficult -torecognize).

In nearly 3 % of Cancer patient's hospital referrals, they clinically present with metastatic disease, without the finding of a known tumor primary site. This last is the CUP definition since the eighties. In some cases, the primary is found at the autopsy, and even in other ones, this procedure also fails in the primary tumor finding!

The above definition is a not wide one, for at that time, many CUPs were not deeply clinically studied for its grim prognosis, with median overall survivals of less than 6 months.

CUP is really a fascinating chapter of Oncology for many reasons on the way.

The most prevalent histology are the adenocarcinomas, followed by squamous cell ones and then others such as melanomas, neuroendocrine tumors, etc.

Most of the CUP metastatic adenocarcinomas if they are supradiaphragmatic, they correspond nearly always to lung cancer and if under diaphragmatic are occult pancreatic cancers. Some of the before-mentioned adenocarcinomas are poorly differentiated and this last is a special entity for it responds very satisfactory to Chemo schedules.

Conventional light microscopy histology is closely helped by immunohistochemistry (IHC) in the study of this Cancer entity.

The knowledge first, about intermediate microfilaments allows the discovery of epithelial tumors where cytokeratin's are present, and classic electron microscopy is also an important additional in the diagnoses.

Cytokeratin's (CK7; CK20, etc.), can separate which are GI Cancers, from those which correspond to lung for e.g., and important to mention the presence also of nearly 14 additional IHC markers such as TTF1 (lung, Thyroid), etc.

Nowadays there are additional pathologic diagnostic tests in the study of CUPs such as gene-expression-based tissue of origin testing, molecular tumor profiling, next generation sequencing. The molecular and genomic profiling is helping in the identification of driver mutations amenable to targeted therapies.

There are many CUPs subsets with favorable clinical and therapeutical outcomes, just to mention a few ones: women with peritoneal carcinomatosis: rule out an ovarian or fallopian tube cancers; women with axillary lymph node metastases: rule out Breast cancer; men with elevated PSA: rule out prostate; Extragonadal germ cell metastases: rule out testicular cancer or a primary extragonadal tumor, patients with a metastatic cervical lymph node, a squamous cell head and neck cancer has to be ruled out.

The science fascination of CUP comports many features. The first one, why an occult extremely low volume tumor, even undetectable by a CT scan or even a PET, can give rise to such metastatic disease burden in different organs. Probably genetic and epigenetic mechanisms are involved in the early metastatic cascade. Surely cells with the necessary genetic mutations to allow them to shed, circulate and colonize other organs. What is known at the present time is that mutations in P53 aren´t involved as drivers in the process.

Tumor microenvironment (TME) features are also allowing this, "calling Mets" for the invasion of different organniches.

Awesome like the above-mentioned is the fact that CUPs comport sometimes, unusual patterns of clinical Mets. They comport not in the way as smartly explained in 1889 by Paget, who published: "Distribution of secondary growths in cancer of the breast", to answer the question, "What is it that decides what organs shall suffer in a case of disseminated cancer?". He scrutinized the autopsy records of 735 women with fatal breast cancer and was struck by the discrepancy between the relative blood supply and the frequency of metastasis in some organs. He commented especially on the high incidence of metastasis in the liver, ovary, and specific bones, and the low incidence in the spleens.

In CUPs for e.g., pancreatic cancer can present with lung Mets or bone Mets; Prostate Cancer with lung and supraclavicular lymph nodes Mets and some other examples also exists found at autopsies, for e.g., renal metastases from breast cancer.

Why, in some of these CUP cases the hypothesis of the seed and soil enunciated by Paget doesn´t apply here totally. Is again to think in TME issues, probably; have we to think in different "genius" genetic programmed tumor cells in the low volume tumor organ with an initial enormous potential for clonality and subclonality?

This last can be "validated" by the melanoma model. A very small visible primary melanoma has a high burden of clonality and subsequent clonal evolution. With the before—mentioned, metastases "come easy everywhere".

Finally, the theory of tumor spontaneous regression of the primary in CUPs.

Spontaneous regressions have been reportedly for renal cancer, melanoma, low-grade lymphomas and neuroblastoma.

So, if this is exact, in CUP's not even find at autopsy, the regression existed, or the tumor was so small to be detected or the organs' cuts weren´t enough to discover the primary (for this last we have to call Dr Barcat!).

As in every Medical discipline, the multidisciplinary team is the "remedy" for the best clinical achievements.

CUPs still deserve a lot of basic, translational, tailored and clinical investigations. We wait for the day to treat this kind of entity at best, trying first to rule out the subset of patients' responders, the exceptional responders with peculiar histologies, and mainly trying to prolong the short-term survival of the difficult-to-treat-ones with the amelioration of their quality-of-life issues.