Letter to the editor

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Letter to the editor

Dear editor:

To begin with, we would like to tell you that it has been a pleasure for us to read the article called, "A review of metastatic cancer with unknown primary cancer". This review, published in the latest issue, makes an excellent approach to neoplasms of undetermined origin, both clinically and paraclinically. This has motivated us to make certain complementary notes in a respectful manner, especially in regards to immunohistochemistry.

As our first point, we would like to highlight that, before performing an immunohistochemistry panel of tests, the pathologist reviews the case and its morphological characteristics in basic histochemical staining to approach the possible origin of the neoplasm (It has been reported that, from this perspective, the origins of 50% to 55% of tumors can be identified). Within this percentage it is possible to perform an appropriate and better directed immunohistochemistry panel. (1).

In case the initial morphology is difficult, the approach is to use immunohistochemical stains. If reactivity with the cytokeratin cocktail (CK AE1/AE3) is demonstrated at this point, the prudent next step is to stain for cytokeratins 7 and 20 (CK7, Ck20) in order to recognize probable primary organs according to the complements marked by these antibodies, as you highlight in Table 5 of the article. At this point, we would like to complement said table and the probable organs according to the variety of markers, as follows (1):

- If the marker is CK7 +/CK20, in addition to the lung and the breast, other possible origins include gynecological organs, salivary glands, thyroid glands and mesothelioma.
- If it is CK7-/CK20 +, possible origins include the colon, the loop of the small intestine, the bladder, the appendix and Merkel cell carcinoma.
- If it is CK7-/CK20-, in addition to the prostate possible origins include the kidney and liver as well as squamous cell carcinoma, neuroendocrine carcinomas and germ cell tumors.
- If the marker is CK7 +/Ck20 +, possible primary sources include adenocarcinomas of the pancreas, stomach or esophagus, mucinous carcinoma of an ovary, urothelial

carcinoma, adenocarcinoma of the small intestinal loop and mucinous adenocarcinoma of the lung. (1)

At this point, and with some of the immunostaining profiles previously mentioned, an additional panel of antibodies should be used for testing that focuses more on the organ indicated by the evaluation of the initial morphology combined with the first panel of immunohistochemistry. At this point of the diagnostic approach, we would like to complement some specific situations.

For example, in the presence of probable thyroid origin - which is important, as you very correctly mention, TTF-1 markers and the thyroglobulin should be used. However, the use of a transcription factor called PAX8 has grown. It is also useful for differentiating kidney, thymus gland, thyroid gland and gynecological origins. PAX8 is the only immunomarker that shows reactivity in anaplastic thyroid carcinoma, since it loses its marking for thyroglobulin and TTF-1 in the vast majority of cases. (1, 2)

Regarding germ cell tumors, in addition to the markers mentioned in the article, a transcriptional regulator of pluripotent cells known as SALL4 is currently widely used. It is an excellent screening marker for germ cell tumors including seminomas, embryonal carcinomas and yolk sac tumors. Its sensitivity for these three is close to 100%. It is also used for choriocarcinoma, regardless of whether it originated from a testicle, ovary, mediastinum, central nervous system or if its origin is metastatic. This is a contrast to OCT4 which is negative for yolk sac tumors. SALL4 has also been described with a rare labeling (<5%) for mammary, prostate, colorectal and squamous cell carcinomas. (3)

Finally, we would like to point out a differentiation marker that has been used lately in daily practice by pathologists primarily for diagnosis of squamous cell carcinoma. We are talking about P40 which recognizes isoforms of P63 and has slightly greater sensitivity and specificity than does the previous last marker. (4) Therefore, the combination of high molecular weight cytokeratins, such as CK5/6, P63 and P40, is very useful and is very sensitive and specific for the diagnosis of squamous cell carcinoma or carcinomas with squamous differentiation.

We hope that these annotations are a great contribution to colleagues and other professionals in the scientific community.

Thank you very much for your attention.

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Response to letter to the Editor

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Dear Editor:

We greatly appreciate the interest of Doctors Baracaldo and Melo in our article, "A review of metastatic cancer with unknown primary cancer" that was published in this magazine. (1)

We agree with their notes complementing Table 5 which lists probable primary tumors according to whether tests are positive or negative for CK7 and CK20. However, it is necessary to make the following clarification.

1. In cases of CK7 +/CK20- marking, the possibility of gynecological primaries must be taken into account. (2)
2. In cases of CK7-/CK20 +, the possibility of Merkel cell carcinoma should be taken into account. Although it is a rare disease, it can account for 10% to 20% of cases of cancers with unknown primaries. (3)
3. In cases of CK7-/CK20-, renal cancer, hepatocellular carcinoma, squamous cell carcinoma, neuroendocrine carcinomas and germ cell tumors should be considered as options. (2)
4. In cases of CK7 +/CK20 +, the possibility of stomach cancer should be taken into account even though it is not usually an unknown primary. (4) It goes without saying that, in Colombia, dyspepsia in a patient over 35 years of age requires endoscopy of the upper digestive tract.

Although cancer of the small intestine, (5) bladder, (6) appendix, (7) thyroid glands, (8) mesothelioma, (9) salivary glands, esophagus, and mucinous carcinoma of the lung may have CK7 and CK20 profiles that could be included in Table 5, they are a rare causes of metastatic cancer with unknown primary (in which the primary lesion is not identified despite standardized diagnostic approach) which was the subject of our review. (10)

In addition, according to the findings in each case, immunohistochemical markers not included in this review such as calretinin, EMA, keratin 34 Beta E12, E-cadherin, CD117, inhibin, caldesmon, calponin, osteocalcin, and CD99 may be requested. The purpose of our review was to describe the general aspects of immunohistochemistry in the treatment of metastatic tumors with unknown primary cancer. Deepening our

understanding of immunohistochemistry is an absolutely extensive topic about which there are treatises. (11, 12)

Again, we appreciate the pertinent comments of Dr. Baracaldo and Dr. Melo. We would also like to highlight that the approach to, and management of, tumors with unknown primaries is complex and involves the participation of several specialists. Of these, a pathologist is fundamental. We are pleased with the interest of these young pathologists in this scenario because they have emphasized that a good pathologist is fundamental and decisive in these cases. For our environment it would be desirable and relevant to have all of the various immunomarkers available in our referral laboratories.

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