CORRESPONDENCE

Cup Syndrome—Metastatic Malignancy With Unknown Primary Tumor

by Dr. med. Gregor Zaun, Prof. Dr. med. Martin Schuler, Prof. Dr. med. Ken Herrmann, and Prof. Dr. med. Andrea Tannapfel
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p16 Examination Is not Sufficient

The explanation of diagnostics required for CUP syndrome, for neck metastases without detectable primary tumor, is incomplete (1). Immunohistochemical examination using the p16 protein is inadequate. The confirmation of p16 is used exclusively to detect oropharyngeal carcinomas and not—and the article does not make this clear—to generally confirm squamous cell carcinomas of the head and neck. The authors did not mention nasopharyngeal carcinoma as an important location of the primary tumor. The current 8th edition of the TNM classification requires for the purpose of diagnosing cervical CUP syndrome to test for the Epstein-Barr virus (EBV), typically by using in-situ hybridization (2). In this way, CUP syndrome with a primary tumor in the nasopharynx can be confirmed or ruled out. Furthermore, the sensitivity for finding the primary tumor by combining p16 confirmation and testing for EBV in the neck metastasis seems superior to positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) (3).

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Palliative Care Was not Considered

The authors presented a review article of "conventional and innovative diagnostic methods [. . .] and highly refined therapeutic strategies to patients with CUP" (1). They describe the highly palliative situation of patients with mean survival times of 8–11 months and 2-year survival periods of only 20%. The recommendation is to give these patients platinum-based chemotherapies, which—while prolonging their remaining lives to such a minimal extent that the purpose of using such therapies is questionable—have substantial adverse effects and lead to impaired quality of life.

On the other hand, they do not make any mention whatsoever of patients' early referral to palliative care services, which support the quality of life and remaining lifespan in exactly this group of patients—and has been internationally recommended for years. In the article, the word "palliative" is mentioned only in association with radiotherapy. Symptom control, quality of life, or even the wishes of patients with a terminal illness do not count. What was not discussed is the fact that chemotherapy does not benefit patients in the last six months of their lives, irrespective of the extent to which their tumor disease had already impaired them (2).

In view of the heterogeneous CUP group, it is incomprehensible that expensive new antibodies are considered a "modern therapeutic concept." Even in well-known indications, only 2.9% (!) of recently licensed modern cancer treatments whose long-term use has been investigated in a study contributed in any way to extending patients' lives and improving their quality of life (3).

Recommending expensive modern therapeutics outside clinical studies, without confirmed benefit and with harm, without providing information on comprehensive palliative care as an alternative contravenes each and every one of the four medical ethical principles.

The vast majority of the patients in a palliative situation wants therapy that targets the symptoms and supports quality of life. For this reason, the review article is probably useful only for the cancer industry and a minority of patients—and the latter mostly has unrealistic expectations of what therapy can deliver (4).

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In Reply:

We thank Prof. Guntinas-Lichius for his comments. In the rare cases of cervical lymph node metastases where in spite of all interdisciplinary methods (including panendoscopy and imaging) no primary tumor can be found, measuring the p16 protein level and testing for HPV (human papillomaviruses) as well as EBV (Epstein-Barr virus) in the tumor cells may be helpful and confirm a nasopharyngeal carcinoma. The TNM classification recommends applying the classification for nasopharyngeal cancers in cases where it is definitely not possible to identify a primary tumor and where the patient has tested positive for EBV. However, the subject here is only classification/staging, not the clinically relevant situation of the question of what should guide treatment.

For reasons of space, in our review article we did not explain nasopharyngeal cancers, which are rare in our latitudes (annual incidence 0.3–0.7/100 000 population) (1). In contrast to EBV positivity of the nasopharyngeal cancers in endemic areas, the

virus is almost always absent from the (keratinized) nasopharyngeal cancers in our own regions, which are not among the relevant endemic areas. Classic histology of a nasopharyngeal carcinoma—also in lymph node metastases—therefore in most cases allows an indication of this tumor entity. Furthermore, the 2017 article by Cheol Park et al. cited by Prof. Guntinas-Lichius mentions a total of 54 patients, of whom only two tested positive for EBV, and only one patient had a nasopharyngeal cancer, whereas no tumor was found in the second patient. Ultimately, this article too ascribes the greatest sensitivity for the detection of the primary tumor in squamous cell carcinomas of the head and neck not to an individual examination but to a combination of the biomarkers HPV, EBV, and p16, as well as 2-deoxy-2-(^{18}F)fluoro-D-glucose positron emission tomography/computed tomography (FDG-PET/CT).

We can only agree with Dr. Thöns regarding the importance of palliative medical care in disseminated CUP syndrome. However, this applies to all cases of advanced tumor disease (and many other non-malignant disorders), and not only to CUP syndrome. However, in our opinion, this important cornerstone of the therapy of tumor patients—whether as palliative treatment in addition to radiotherapy or medication or as mere "best supportive care" treatment—does not have any place in a review article of the current therapeutic options for CUP syndrome, but only in a separate, detailed article on palliative medicine.

It goes without saying that in patients with advanced tumor disease—and thus also in advanced CUP syndrome—general palliative medical measures should always be considered. And of course, in very advanced CUP syndrome, purely palliative treatment measures in the sense of "best supportive care" need to be discussed with the patient if no treatment options of greater usefulness are available—but only if that is the case.

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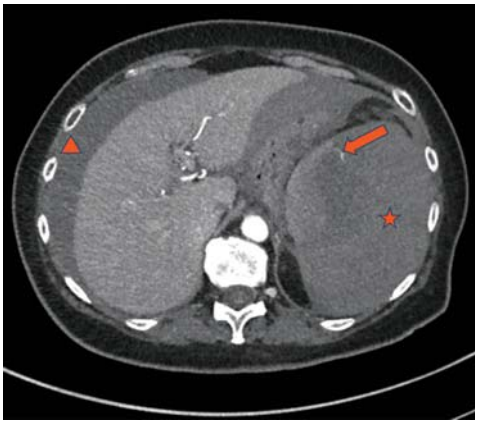
CLINICAL SNAPSHOT

Think of Rare Things—Atraumatic Splenic Hemorrhage

A 58-year-old woman complained of upper abdominal pain radiating into the left shoulder. She had previously suffered from recurrent bouts of alcoholic pancreatitis, and the serum pancreatic amylase was elevated; a new bout of pancreatitis was initially suspected. Ultrasonography revealed a small amount of peripancreatic free fluid. There was no history or physical evidence of trauma. The patient became intermittently hemodynamically unstable, and her hemoglobin level fell. Vascular erosion was suspected. CT angiography of the abdomen revealed a spontaneous atraumatic splenic hemorrhage *(Figure)*, which was treated in an interventional radiological procedure. The patient went on to a full recovery.

Atraumatic splenic hemorrhage is rare compared to traumatic splenic hemorrhage. 7% of cases are idiopathic and 93% arise in the setting of other diseases, particularly immunological, hematological, or neoplastic conditions, or after invasive diagnostic procedures. An association between chronic pancreatitis and spontaneous splenic rupture has been documented in published case series. This patient's major symptom is known as Kehr's sign. The condition is primarily diagnosed with ultrasonography and/or computed tomography and treated either with an interventional radiological procedure or by splenectomy.



Computed tomography of the upper abdomen after the intravenous administration of contrast medium
There is a subcapsular splenic hematoma (star) with active bleeding (arrow), as well as hematoperitoneum with perihepatic free fluid (triangle).

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