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Carcinoma of unknown primary site (CUPS): case series.

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1. INTRODUCTION

Background:Carcinoma of unknown primary sites(CUPS)are group of malignancies which present with widespread metastasis without an identifiable primary.3 -5% of all malignancies can present as CUPS. The clinical behavior of these cancers is usually aggressive and prognosis remains poor.

Materials and methods:From January 2023 toaugust 2025,total 19 cases of CUPS were registered in our department for whom the data were collected and analyzed.

Results: Median age at presentation of our patients was 51 years(27 -75 years). 42.1 %(n=8) were females and 57.9 %(n=11) were males. Mean ECOG PS of patients was 2±1.1. Median number of sites involved were 2(1-5).In 26.3%(n=5) patients site of biopsy was lymphnode,21%(n=4),from liver and 10.5%(n=2) were diagnosed by fluid cytology . Morphologically 63.2% (n=12) biopsies were adenocarcinoma,15.8%(n=3) poorly differentiatedcarcinoma,10.5%(n=2) poorly differentiated squamous cell carcinoma,5.3%(n=1) each as poorly differentiated adenocarcinoma and adenoid cystic carcinoma.

After immunohistochemistry (IHC) amongst the 12 adenocarcinoma patients CK7 was positive in 58.3%(7/12),CK20, PanCK in41.6%(5/12)each,CK19in25%(3/12)andCDX2andTTF1in8.3%(1/12).

Poorly differentiated squamous cell carcinoma and adenoid cystic carcinoma histology had 100% P63 positivity. Poorly differentiated carcinomas showed PanCK positivity in 66.6%(n=2),EMA and TTF1 positivity in 33.3%.PET CT was done in 15.7 %(n=3).Primary was apparent in only 2 out of 19 cases (10.5%).After diagnosis 11 patients received chemotherapy, 2 patients received Radiotherapy (1 palliative and 1 radical dose) and 3 patients underwent surgery. Among 11 patients who received chemotherapy median number of chemotherapy cycles given was 4(1-7). 45.4% (n=5) received gemcitabine based chemo, 36.3 %(n=4) paclitaxel and carboplatin, 18 %(N=2) received capecitabine and oxaliplatin.36.3%(N=4)completed the desired number of chemotherapy cycles with 50% CR and 50% PR rates.3 out of 8 patients who were not candidate for chemotherapy received empiricalgeftinib. Median follow of our study was 11.4 months with median progression free survival (PFS) of 6.7±3.2 months (95% CI 0.37 -13.0), median overall survival (OS) 6.9±3.2 months (95%CI 0.57 -13.2).

2. DISCUSSION:

The pursuit of further diagnostic studies like pan endoscopy, whole body PET CT scan, EUS, ERCP, capsule endoscopy will help in identifying the primary site of malignancy. CUPSusually classified into four major subtypes (well or moderately differentiated adenocarcinoma (50%), poorly differentiated or undifferentiated adenocarcinoma (30%), squamous cell carcinoma (15%), and undifferentiated neoplasms (5%), neuroendocrine tumors of unknown primary(1%). In patients with differentiated adenocarcinoma or undifferentiated carcinoma, 70% of patients have been found to have chromosomal instability (aneuploidy), a finding similar to that reported for adenocarcinomas of known histogenesis. Immunohistochemical studies, including the immunoperoxidase technique using a series of monoclonal or polyclonal antibodies to enzymes, structural tissue components (i.e., cytokeratins; CK), hormonal receptors, hormones, oncofetal antigens, or other substances, are useful for cell-type determination and pathologic diagnosis in patients with occult primary tumors. In particular, the cytokeratins CK7 and CK20, two intermediate filament proteins whose expression patterns are closely associated with tissue differentiation and lineage within epithelial cells, are the two most commonly

used immunostains for differentiation of occult primary tumors into subsets of carcinomas. While the NCCN does encourage the next-generation sequencing (NGS) for unknown primary tumors, at present, they state there is no prospective data to support the use of biomarker-driven therapy beyond FDA-approved therapeutics approved for tumor-agnostic aberrations. Patients with CUP may present with an unfavorable or favorable set of prognostic signs [19]. Treatment and response vary by histology and favorability of subtype. Localized adenocarcinoma of unknown primary should be treated according to the most likely primary site. A previous study identified that patients with a favorable CUP subtype experienced superior overall survival compared to those with unfavorable subtypes (36.6 months vs. 3.8 months) [20]. Current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), based on all available data, recommend mostly platinum-based systemic chemotherapy regimen approaches as the first-line option in our case, with the exception being FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin) which can be considered in cases of presumed GI primary site. Limition I our study was NGS and molecular profiling was not done for all patients. This might impact treatment options and survival of patients.

Conclusion: In our study the similar PFS and OS was probably because of less clear distinction between progression and death and shorter follow up period. Though not able to find a primary site is an obstacle for deliveringsitespecificchemotherapyinmajorityofpatients, still in a subset therapy can be tailored as per the tissue of origin. NGS and molecular profiling is mandatory for all CUPS patients will help in guiding treatment.

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