A Case of Bladder Large Cell Carcinoma with Review of the Literature

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Abstract
Neuroendocrine (NE) tumors of the bladder are infrequent. Among them, large cell NE tumor has been outlined only in case reports and short case series, which describes them as aggressive malignancies with dismal prognosis requiring a multidisciplinary approach. The case of an 82-year-old patient with muscle-invasive large cell NE carcinoma of the bladder associated with urothelial carcinoma in situ is presented. Despite combined treatment modality, relapse with metastatic disease was detected 12.5 months after the initial diagnosis. Thereafter, we review several published cases, and results of the collected data are compared with the largest studies published on this topic.

Case Presentation
An 82-year-old nonsmoking woman with multiple geriatric syndromes presented with gross hematuria and urgency. Subsequently, she underwent cystoscopy that revealed two 1.5 cm in diameter lesions on the posterior wall. A transurethral resection (TURB) was performed, and pathology was consistent with a large cell neuroendocrine (NE) carcinoma (LCNEC) invading muscularis mucosa, associated with urothelial carcinoma in situ. Computed tomography of the chest, abdomen, and pelvis was unrevealing. Staging was completed with fluoro-deoxyglucose positron emission tomography (FDG-PET) scan that confirmed no evidence of
metastatic or nodal disease. Patient declined radical cystectomy. Due to marginal performance status, carboplatin with AUC of 5 mg/mL min and etoposide 100 mg/m² for 3 cycles was administered. Consolidation with chemoradiotherapy employing weekly carboplatin AUC of 2 mg/mL min was administered concurrently with 45 Gy radiation therapy of the pelvis and a 9 Gy boost to the tumor volume. Patient tolerated treatment without unexpected side effect. Surveillance with cystoscopy and computed tomography scan at 3, 6, and 9 months demonstrated no evidence of disease. Patient developed recurrence with bone, nodal, and liver metastases 1 year after completion of definitive treatment. Ultrasound-guided liver lesion biopsy revealed LCNEC. No local recurrence was noted at cystoscopy. Given 1 year since last platinum exposure, she was offered palliative chemotherapy (CT) employing carboplatin and etoposide.

Literature Review and Discussion

Introduction

Bladder cancer is estimated to account for over 83,000 cases in the USA and over 17,000 deaths in 2021, being the 4th most common cancer in men and the 6th overall. Of those cases, NE tumors represent less than 1% [1]. According to the 2016 WHO classification, primary NE neoplasm of the bladder can be subdivided into 4 main groups: small cell NEC (SCNEC), LCNEC, well-differentiated NE tumor, and paraganglioma [2]. SCNEC constitutes most of the bladder NE malignancies, while LCNEC is the least common subtype, which has been mostly described in case reports or small case series. The first case of LCNEC was first described in 1982 by Abenoza et al. [3], but it is reasonable to argue that before that report it was misdiagnosed as undifferentiated urothelial carcinoma. Not infrequently, LCNEC is accompanied by smaller population of neoplastic cells of other histology, including SCNEC, urothelial carcinoma, or adenocarcinoma, squamous carcinoma, as well as sarcomatoid carcinoma.

The origin of NE tumor of the bladder is also a matter of debate, and different theories have been proposed, including the multipotent stem cell hypothesis, which could account for the concomitant presence of other tumoral populations in the sample [4–6]. Due to its rarity, there are still no guidelines regarding treatment of LCNEC. We hereby present a review of the literature focused on the management of this rare malignancy, to provide a benchmark reference for the management of future patients by genitourinary specialists.

Methods

To identify the articles present in the literature, we searched the PubMed and Google Scholar databases using the following words: “bladder cancer,” or “large cell carcinoma,” or “neuroendocrine bladder.” Moreover, the bibliography of all appropriate studies was consulted to identify further pertinent works, and hand searching was also done to identify potentially relevant, nonindexed studies. Data regarding age, sex, histology (pure vs. mixed), TNM stage, treatment approach (single mode vs. multimodal treatment, conservative vs. radical surgery), and survival were assessed and collected in the online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000521607). Median was calculated for age and survival, while percentage was analyzed for the remaining variables. The Fisher exact test was performed to assess the association between variables.

Results

Thirty-seven original reports or case series were identified [3, 7–42], accounting for 122 patients, spanning from 1986 to 2021. We then included our case, for a total of 123 patients. One study analyzing data derived from the Surveillance, Epidemiology, and End
Results database was not included, due to the potential overlap with other studies [43]. Among the 122 patients identified, most of the data of interest were available for 70 patients. Two studies [33, 36] accounting for 51 patients in total and 2 case reports [13, 28] were excluded: the first two grouped together data from all NEC, while the last two either lacked an English manuscript or did not include any of the data of interests, respectively (Fig. 1). Median age for the series was 64.5 years (20–84) and 51/67 (76%) were men. Histology was available for 65 patients, of which 30 (46%) were pure LCNEC. Thirty percent (21/70) were metastatic at diagnosis. For the remaining 49 patients with locally advanced disease, T stage was reported for 28 cases: 12 with T1-2, 16 with T3-4. Management was reported for 68 patients. A total of 60 patients (88%) received surgery (i.e., TURBT, partial, or total cystectomy) either alone or in combination with other treatment modalities, and a radical approach was preferred in 57% of cases (34/60). For those who did not receive surgery, 5 received either CT, radiotherapy (RT), or a combination of both, while 3 patients experienced a rapid decline before receiving any treatment and were managed with supportive care only. Multimodal treatment combining surgery with CT (either in the adjuvant or neoadjuvant setting) ± RT was the most adopted approach, selected for 30 patients without distal metastasis (61%). Analyzing the treatment modality for patients with LCNEC over time, a trend toward increased use of multimodal approach for limited stage disease was detected: in the timeframe 2019–2021, 79% (15/19) of patients with limited stage disease received a combination of surgery and CT, as opposite to approximately 50% (15/30) for older reports. The choice of the CT agent administered was reported for 19 cases and platinum-based regimens were used in all patients (M-VAC = 3; cis-platin + gemcitabine = 2; cis-platin + etoposide = 6; carboplatin + etoposide = 5; unspecified platinum-based regimen = 3). Outcome (i.e., death vs. alive) was instead available for 67 patients. Of them, 39% (26/67) were alive at their respective data cutoffs. Among those with metastatic disease at diagnosis, only 1 (5%) was reported to be alive [42], versus 24 (52%)

Fig. 1. Consort diagram of the identified and selected studies. NEC, neuroendocrine carcinoma.
of the nonmetastatic patients \( (p = 0.0001) \). In the latter group, 83% with T1-2 stage were alive, as compared to 38% with T3-4 disease \( (p = 0.02) \). Survival data were available for 59 patients, with a median survival of 12.25 months for the whole series (0.5 months to 11 years) (see Table 1 for additional information). Median survival for patients without distant metastasis receiving multimodal treatment was 20 months versus 8 months for those who were managed with surgery alone. For patients who received multimodal approach, surgery (either conservative or radical) combined with cis-platin + etoposide (either in the neoadjuvant or adjuvant setting) was associated with a more favorable outcome (median survival 31 months, vs. 16 months for surgery + carboplatin and etoposide). In regard to the surgical approach, the median survival for patients receiving a radical cystectomy was 20 months (vs. 12 months for conservative surgery).

**Discussion**

We presented a comprehensive overview of the cases of LCNEC available in the literature, which, to our knowledge, represents the largest collection ever reported in the literature. According to the data reviewed, LCNEC is an aggressive disease, which is more frequent \( (3 \times) \) in men than women. It is generally diagnosed in the elderly population, with a median age of 63 years, and it almost universally presents as muscle invasive \( (88\%) \), and frequently metastatic \( (30\%) \), at diagnosis. Oncological outcomes for affected patients are still poor, with a median survival among the cases we analyzed of only 12.25 months and 38% of patients still alive at the respective data cutoffs. The presence of metastasis was a strong determinant of survival, but the depth of bladder invasion appeared also associated with higher percentage of survival. A more favorable outcome was noted among patients who received radical surgery and multimodal treatment, suggesting that these complex and generally frail patients may greatly benefit from a multidisciplinary approach.

As noted in the previous section, three studies were not included in our analysis for the abovementioned reasons; however, they are pivotal in the clinical characterization of LCNEC since together with the study of Wang et al. [40] they are the largest on the topic. Specifically, Niu et al. [43] analyzed data on bladder NECs derived from the Surveillance, Epidemiology, and End Results database, including 35 patients with LCNEC, while Sroussi et al. [36] and Zhou et al. [33] retrospectively evaluated patients treated in French institutions and 4 Chinese hospitals. Similarly to our findings, patients were mostly elderly male, with a disease that was almost always muscle invasive at diagnosis. "Pure" LCNEC constituted 36–48% of cases, which is comparable to what we also observed in our review. The prognostic significance of the "pure" versus "mixed" histology is not clear. Wang et al. [40] found a worse prognosis for patients displaying a pure histology \( (3.5 \text{ vs. } 40.5 \text{ months for mixed}) \). However, in their systematic review of the literature, Xia et al. [37] did not find any association between survival and histology. Likewise, we did not find any difference between pure and mixed LCNEC in terms of outcome (data not shown). The prognostic value of staging was also assessed. Although metastasis was unequivocally associated with a worse prognosis [33, 36, 37, 40, 43], impact of different stages was less easy to assess given the rarity of the disease and most of the studies who did it pooled together data of LCNEC and SCNEC [36, 43]. Studies which focused exclusively on LCNEC yielded controversial results [34, 37]. In our analysis, limited stage appears associated with improved outcome compared to T3-4, and this association was statistically significant.

As previously stated, treatment of LCNEC is largely based on the experience with its lung counterpart and on the more common SCNEC of the bladder [44–51]. A common finding that all major reports highlighted is the benefit of multimodal therapy over single modality [30, 34, 36, 37, 43], with a major role of CT either in the adjuvant or neoadjuvant setting [36, 37, 43], which is in line with the current evidence on SCNEC of the bladder.
Table 1. Identified studies in the literature describing cases of LCNEC in order of publication

| Article          | Year of publication | Patients, n | Age | Sex | Pure versus mixed | TNM staging | M0 versus M1 | Multimodal treatment versus surgery alone | Conservative versus radical | Outcome | OS      |
|------------------|---------------------|-------------|-----|-----|-------------------|-------------|--------------|------------------------------------------|-----------------------------|---------|---------|
| Abenoza et al. [3] | 1986                | 1           | 55  | 0   | 0                 | T3N+        | M-           | MM                                       | R                           | 0       | 30 mo   |
| Hailemariam et al. [7] | 1998            | 1           | 73  | 0   | 1                 | T3N-        | M-           | S                                        | R                           | 0       | 2 mo    |
| Dundr et al. [8]  | 2003                | 1           | 54  | 1   | 0                 | T3N-        | M-           | MM                                       | C                           | 1       | 16 mo   |
| Li et al. [9]     | 2004                | 1           | 61  | 0   | 0                 | T2N-        | M-           | S                                        | C                           | 1       | 8 mo    |
| Quek et al. [10]  | 2005                | 5           | 72  | 0   | 2                 | 1 T2, 4 M+  | 4 M+, 1 M- | 1 MM, 4 NA                               | NA                          | 1 alive, 4 dead | 1 yr, 4 NA |
| Evans et al. [11] | 2006                | 1           | 82  | 0   | 0                 | T2N-        | M-           | MM                                       | C                           | 1       | 24 mo   |
| Lee et al. [12]   | 2006                | 1           | 32  | 0   | 1                 | T3N-        | M-           | MM                                       | C                           | 0       | 12 mo   |
| Quek et al. [10]  | 2007                | 2           | 41.5| 1   | 2                 | 1 stage 2, 1 stage 4 | 1 M+, 1 M- | 2 MM                                     | R                           | 1 alive, 1 dead | 12.5 mo |
| Akamatsu et al. [15] | 2008              | 1           | 63  | 0   | 0                 | T3Nx        | M-           | MM                                       | R                           | 1       | 16 mo   |
| Bertacini et al. [16] | 2008             | 1           | 37  | 0   | 1                 | T3N+        | M-           | MM                                       | R                           | 1       | 20 mo   |
| Lee et al. [17]   | 2009                | 1           | 20  | 0   | 1                 | NA          | M-           | MM                                       | C                           | 0       | 14 mo   |
| Oshino et al. [18] | 2010              | 1           | 76  | 1   | 1                 | T2          | M-           | S                                        | R                           | 1       | 48 mo   |
| Martin et al. [19] | 2011              | 1           | 69  | 1   | 1                 | T2N-        | M-           | S                                        | R                           | 1       | 12 mo   |
| Tsugu et al. [20] | 2011                | 1           | 74  | 0   | 1                 | NA          | M+           | S                                        | None                        | 0       | 5 mo    |
| Engles et al. [21] | 2012               | 1           | 65  | 0   | 0                 | T2          | M-           | MM                                       | R                           | 1       | 3 mo    |
| Hata and Tasaki [22] | 2013              | 1           | 84  | 0   | 0                 | T1          | M-           | S                                        | C                           | 1       | 8 mo    |
| Colarossi et al. [23] | 2013              | 1           | 53  | 1   | 0                 | T3n2        | M+           | MM                                       | R                           | 0       | 7 mo    |
| Coelho et al. [24] | 2013               | 2           | 58  | 0   | 0                 | 1 T3N+ M0, 1 M+ | 1 M+, 1 M- | 2S                                       | C                           | 0       | 1.7 mo  |
| Sari et al. [25]  | 2013                | 1           | 67  | 0   | 0                 | T2nx        | M-           | S                                        | C                           | 0       | 0.5 mo  |
| Pusid et al. [26] | 2014                | 1           | 68  | 0   | 1                 | NA          | M-           | S                                        | R                           | NA     | NA      |
| Bhatt et al. [27] | 2014                | 6           | 68  | 2   | 3                 | NA          | 3 M+, 3 M- | 5 MM, 1 S                                 | 4 R, 2 C                    | 5 dead, 1 alive | 21 mo   |
| Radovic et al. [29] | 2015               | 1           | 58  | 0   | 1                 | NA          | M+           | S                                        | R                           | 0       | 5 mo    |
| Gupta et al. [30] | 2015                | 5           | 77  | 1   | NA                | 3 T3a, 2 T4a N0 | 5 M-   | 1 MM, 4 S                                 | 5 R                         | 5 dead, 1 alive | 1.96 yr, 4 NA |
| Chong et al. [31] | 2017                | 1           | 72  | 0   | 1                 | T4n+        | M-           | S                                        | R                           | 1       | 36 mo   |
| Article                      | Year of publication | Patients, n | Age | Sex | Pure versus mixed | TNM staging | M0 versus M1 | Multimodal treatment versus surgery alone | Conservative versus radical | Outcome | OS |
|-----------------------------|---------------------|-------------|-----|-----|-------------------|-------------|--------------|------------------------------------------------|----------------------------|---------|-----|
| Zakaria et al. [32]         | 2017                | 1           | 72  | 0   | 1                 | NA          | M-           | MM                                                             | C                          | 0       | 6 mo |
| Wang et al. [34]            | 2017                | 1           | 25  | 1   | 0                 | T4n1        | M-           | MM                                                             | C                          | 0       | 31 mo|
| Akdeniz et al. [35]         | 2018                | 1           | 45  | 0   | 1                 | NA          | M-           | S                                                              | C                          | NA      | NA  |
| Xia et al. [37]             | 2020                | 1           | 39  | 0   | 1                 | T2n-        | M-           | MM                                                             | R                          | 1       | 59 mo|
| Halabi et al. [38]          | 2020                | 1           | 64  | 0   | 0                 | T2n+        | M-           | MM                                                             | C                          | 0       | 9 mo |
| Goret [39]                  | 2020                | 1           | 70  | 0   | 1                 | T4          | NA           | MM                                                             | NA                         | NA      | NA  |
| Wang et al. [40]            | 2021                | 22          | 74.5| 6   | 8                 | NA          | 8 M+, 14 M-  | 10 MM, 4 S, 3 none, 2 RT, 1 CT, 2 unclear                    | 9R, 5C, 2 unclear, 6 no surgery | 7 alive | 8.5 mo(whole series) |
| Pini et al. [41]            | 2021                | 1           | 49  | 0   | 0                 | T2          | M-           | MM                                                             | R                          | 1       | 24 mo|
| Tili et al. [42]            | 2021                | 1           | 49  | 0   | 1                 | NA          | M+           | MM                                                             | C                          | 1       | 12 mo|
| Our case                    | 2021                | 1           | 82  | 0   | 0                 | T2          | M-           | MM                                                             | C                          | 1       | 12.5 mo|

M-, nonmetastatic; M+, metastatic; MM, multimodal treatment; S, surgery alone; C, conservative surgery; R, radical surgery; mo, months; NA, data not available; yr, years; RT, radiotherapy; CT, chemotherapy.
Namely, Wang et al. [40] reported a median survival of only 8.9 months for nonmetastatic patients who did not receive neoadjuvant CT, while this value was not reached for those treated with a combination approach. Similarly, outcome was dismal in the cohorts of Niu et al. [43] for patients managed with bladder directed therapies only (i.e., cystectomy, 7.03 of median overall survival [mOS]). While these two data were comparable to what we found in our study, reported outcome for patients receiving multimodal treatment was notably superior in some of these analyses [36, 40, 43]. A possible explanation of such discrepancy could be the presence of histologies other than LCNEC in two of these cohorts. Consistently with this hypothesis, in the retrospective analysis of Xia et al. [37] which was focused on LCNEC only, a mOS of 22 months was described for patients receiving multimodal treatment, which is closer to the one we observed (20 months). More controversial is instead the benefit of radical surgery over bladder sparing approach. In our analysis, although the survival rate was similar between groups, median survival of patients receiving radical approach was higher when compared to those managed conservatively (20 vs. 12 months, respectively), but no test was performed to determine the statistical significance of this difference. Both the retrospective study of Sroussi et al. [36] and the systematic review of Xia et al. [37] did not find any benefit of radical cystectomy. On the other hand, the analysis by Niu et al. [43] identified the subgroup treated with a combination of cystectomy, CT, and RT as the one with the best overall prognosis, reaching a mOS of 88 months (vs. 30.98 months for those treated without RT). This controversy holds true also when we look at SCNEC, with some studies arguing in favor of a bladder sparing approach in selected cases [45, 58, 59], while other of radical cystectomy [51, 56]. National Comprehensive Cancer Network (NCCN) guidelines therefore support either radical surgery or TURBT followed by RT or chemoradiotherapy for SCNEC. Given the controversial data on this specific topic, a case-by-case decision should be made, based on patient preference, comorbidities, and fitness. Regarding the choice of the CT regimen, considering the experience with the lung counterpart, the most adopted strategy in the literature is a platinum-based regimen, which was also the choice we made for our patient. Interestingly, one study found a survival advantage for patients treated with cis-platin over carboplatin [36], which is similar to what was noted in the context of urothelial carcinoma, but not in NEC of the lung [60]. Although the extremely limited number of patients does not allow to make any definitive conclusion, a more favorable outcome was noted for patients receiving cis-platin-based CT also in our study. Therefore, it would be reasonable to prefer the first over the latter when the patient fitness allows it, particularly in the setting of a concomitant urothelial component.

This study comes with several limitations. Namely, we analyzed data derived from several reports over a broad range of time. Hence, its retrospective nature and the heterogeneity of patients’ characteristics, diagnostic criteria, and treatment strategies partially affect its validity. Also, a very limited number of statistical tests were performed; therefore, the significance of some findings could not be properly estimated. Finally, the limitedness of the population did not allow to perform any multivariate analysis.

**Future Perspectives**

A promising field, which has been minimally (if none) investigated by the abovementioned studies, is represented by checkpoint inhibitors, which are now an established pillar for the treatment of SCNEC of the lung [61–64], with one retrospective analysis and a basket trial suggesting a role also for LCNEC [65, 66]. Based on these observations, a role of checkpoint inhibitors for NEC of the bladder was hypothesized. Although direct experience with bladder LCNEC is nearly absent so far, results obtained in few patients with SCNEC of the urinary system are promising and could lead to new treatment option for
patients affected by this rare malignancy [67–69]. Moreover, investigating targetable genomic alterations in these patients may help improve their multimodal treatment [6, 70–72]. Indeed, a recent comprehensive genomic profiling study of SCNEC cases identified a high (>10 mut/MB) tumor mutational burden (i.e., a positive biomarker for immunotherapy efficacy) in about 40% of patients, supporting a potential benefit from immune checkpoint inhibitors [71]. On this line, another study on 85 advanced bladder NE neoplasms found actionable somatic aberrations in almost half of sequenced patients [72]. Future studies will hopefully confirm a similar scenario also for LCNEC patients. Notably, one clinical trial (NCT03866382) is currently evaluating the efficacy of nivolumab and ipilimumab with the oral small molecule inhibitor cabozantinib for rare genitourinary malignancies, including LCNEC, and will likely shed more light on the best management options for LCNEC patients.

Conclusions

LCNEC is a rare entity associated with a poor outcome. More efforts are needed to better characterize this disease and understand the best approach to treat it. Current data suggest a benefit of multimodal treatment over surgery alone also for limited disease, but despite that, prognosis remains dismal. Given results with similar malignancies, efforts to determine a role of immunotherapy in this rare tumor are needed.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report. In light of the nature of the study, Ethics Committee/IRB approval was deemed not be required.

Conflict of Interest Statement

The authors state that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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Author Contributions

P.L., A.Y., and O.K. have contributed to the concept of the article; P.L. worked on the acquisition, analysis, and interpretation of data. P.L. drafted the article and A.Y. and O.K. revised it critically. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

The data used to support the findings of this study are included within the article and its online supplementary material.

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