ABSTRACT
Radiological analyses in a 61-year-old patient being followed since 2005 for low-grade, non-invasive urothelial carcinoma (UC) (Ta) revealed a 5-cm pleural-based mass in the lower lobe of the right lung for which a subsequent transthoracic fine-needle aspiration cytology was performed. Upon observing the carcinoma cells consistent with UC metastasis, systemic chemotherapy was commenced. The patient underwent a metastatectomy based on the thoracic computerized tomography scan performed on the 4th month of treatment, which revealed notable regression. The resected tumor was morphologically similar to cells seen in the transthoracic fine-needle aspiration and was immunohistochemically positive for p63, uroplakin, thrombomodulin, CK7 and CK20 at varying degrees but was negative for TTF-1. We report a case of metastatic UC of the lung in a patient who had had a low-grade superficial UC of the urinary bladder and we discuss the cytopathological features of this rare entity in light of the literature.

Key words: Cytology; FNAC; low-grade urothelial carcinoma; lung; metastasis

Case Report
Clinical features
An urothelial neoplasm of the bladder of a 61-year-old male patient, who first presented to the clinic in 2005 with hematuria and was subsequently diagnosed as a low-grade non-invasive UC (Ta), recurred three times during follow-up with similar histological diagnoses. He was treated with transurethral resection (TUR) of the tumor followed by intravesical mitomycin. Radiological analyses performed during routine follow-up 8 years after the initial diagnosis revealed a 5-cm pleural-based mass in the inferior lobe of the right lung and a transthoracic fine-needle aspiration cytology (FNAC) was performed for primary/metastatic tumor differentiation. Observing carcinoma cells consistent with UC metastasis, systemic chemotherapy was commenced. After the first metastatectomy revealed a mass in the bladder, which was again diagnosed as a non-invasive UC. On the 4th month of chemotherapy, a thoracic computerized tomography (CT) scan demonstrated notable regression in the lung mass, prompting a metastatectomy through posterolateral...
thoracotomy. Similar to the cytopathological examination, the histopathological findings were also consistent with UC metastasis.

**Cytopathological features**

Air-dried and ethanol-fixed slides obtained through CT-guided transthoracic FNAC were stained with Diff Quick, May-Grünwald-Giemsa and Papanicolaou stain. During cytopathological examination, tumor cells generally scattered individually or sometimes forming syncytial groups with focal papillary configurations in the form of multi-layered cells arranged around a significant fibrovascular core, were observed [Figure 1]. Tumor cells were uniform round or oval-shaped with wide, eosinophilic and granular cytoplasms, had central or eccentric nuclei with fine chromatin and rare nucleoli [Figure 2]. Intracytoplasmic vacuoles were discerned in a number of cells. There were occasional racket-like cells with eccentric nuclei and small vacuoles forming fishtail-like cytoplasmic extensions in varying lengths [Figure 3]. Immunohistochemically, the tumor cells were negative for TTF-1 and cytopathological findings were interpreted as carcinoma cells consistent with UC metastasis.

**Histopathological features**

In sections obtained from the 5 cm × 3.5 cm × 2 cm sharp bordered mass excised from the lung, solid tumor cell clusters with mild-to-moderate pleomorphism were observed. Occasional foci of lymphovascular invasion were also detected [Figure 4]. On immunohistochemical examinations, tumor cells displayed extensive nuclear reaction with p63 [Figure 5a], focal strong cytoplasmic and membranous reaction with uroplakin [Figure 5b], focal strong cytoplasmic reaction with thrombomodulin and focal–weak cytoplasmic reaction with CK7 and CK20. No reaction was observed with TTF-1.
Discussion

It is generally thought that Ta UC has no potential for lymphatic or hematogeneous spread as the bladder does not contain intraepithelial vasculature. Several iatrogenic mechanisms to explain distant organ metastases in low-grade UC have been suggested:

1. Staging inaccuracies,
2. Intravascular spread of tumor cells during TUR,
3. Basal membrane injury due to intravesicular therapy and,
4. Sampling errors during TUR.\[2,4\]

While the 5-year recurrence rates for low-grade UC range between 31% and 78%, and the progression rate is between 5% and 25% in superficial UCs without muscular invasion, only 24 cases with extensive metastasis have been reported in the literature.\[2,6\] Thirteen of these tumors showed lung metastasis, with liver, bones, ovaries, orbit of the eye, brain and uterine corpus reported as other localizations for metastasis.\[1,2\]

Patients with non-muscle invasive UCs reported in the previous literature with lung metastasis are summarized in Table 1. Observed patterns of lung metastases of non-muscle invasive UC consisted of a solitary mass, multiple cavitary lesions and multiple nodules. Prognosis was reported to be quite well in these patients, who received systemic chemotherapy after complete resection of the pulmonary lesion.\[2,3\] At the latest follow-up, our patient was without evidence of disease.

Considering overall metastatic UCs, there is a limited number of reports in the literature highlighting the cytopathological features of these tumors.\[5,7,8\] Cytopathological features that are used to diagnose these tumors and to differentiate them from other tumors are summarized in Table 2. In general, it is emphasized that the presence of history of UC in the patient’s clinic is the most significant factor in diagnosing metastatic UCs, and these cytomorphological features may be helpful in making a diagnosis.\[9,8\] Multi-layered papillary fragments and cercariform cells are the most frequently highlighted cytopathological features.\[5,7\]

“Cercariform cells” (CCs), which were first described in 1993 by Johnson and Kini and further defined in 1995 by Powers and Elbadawi, are fusiform, pyramidal or racket-like cells with eccentric nuclei that form non-tapering, flattened, bulbous...

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Table 1: Summary of non-muscle invasive urothelial carcinoma cases with lung metastases reported in the literature

| Case | First author (reference) | Year | Age | Sex | Localization of primary tumor | Features of mass | T category† | Histologic grade†† |
|------|--------------------------|------|-----|-----|--------------------------------|-----------------|------------|------------------|
| 1    | Seymour et al.           | 1972 | 33  | M   | Bladder                        | Not available   | T<2        | Grade 2*         |
| 2    | Matthews et al.          | 1984 | 48  | F   | Bladder                        | Not available   | Ta         | Grade 1*         |
| 3    | Matthews et al.          | 1984 | 73  | M   | Bladder                        | Not available   | T1         | Grade 2*         |
| 4    | Matthews et al.          | 1984 | 77  | M   | Bladder                        | Not available   | T1         | Grade 2*         |
| 5    | Koh et al.               | 1994 | 42  | M   | Bladder                        | Multiple cavitary lesions | T1         | Grade 2*         |
| 6    | Hirayama et al.          | 2007 | 66  | F   | Bladder                        | Right upper lung, coin-sized lesion | Ta         | Low grade**      |
| 7    | Haga et al.              | 2008 | 95  | M   | Bladder                        | Left upper lung, a solitary mass | T1         | Grade 3*         |
| 8    | Cimen et al.             | 2007 | 67  | M   | Bladder                        | Bilateral, multiple cavitary lesions | T1         | Grade 3*         |
| 9    | Dougherty et al.         | 2009 | 78  | M   | Bladder                        | Periphery of the right middle lung, solitary two nodules | Ta         | Low grade**      |
| 10   | Dougherty et al.         | 2009 | 61  | M   | Bladder, renal pelvis and left ureter | Right lower lung, multiple lesions | Ta         | Low grade**      |
| 11   | Arai et al.              | 2012 | 52  | F   | Bladder                        | Right upper lung, a solitary mass | T1         | Grade 3*         |
| 12   | Sano et al.              | 2013 | 66  | M   | Bladder                        | Right lower lung, 7.5 cm diameter, a round nodule | Ta         | Low grade**      |
| 13   | Nkwam et al.             | 2013 | 78  | M   | Bladder                        | Left apex of the lung, 10.5 mm diameter, a nodule | Ta         | Grade 2*         |
| 14   | Present case             | 2013 | 61  | M   | Bladder                        | Right lower lung, 5 cm diameter, a round solitary nodule | Ta         | Low grade**      |

†T category staged according to the International union against cancer staging guidelines, ††Tumor grade was evaluated using the WHO 1973* and 2004** grading criteria.
or fishtail-like cytoplasmic extensions in varying lengths.\[^{5,7-10}\]

The presence of a small vacuole in the bulbous tail was also a helpful criterion.\[^{9}\] These cells, which are encountered in 57-100% of metastatic UCs, are interpreted in favor of UC, particularly when they are observed in large numbers.\[^{7,9,10}\]

It has been emphasized that they can be encountered in other tumors in small numbers, i.e. they are not specific, and must be considered alongside other clinical and morphological characteristics, keeping in mind that it is difficult to differentiate metastatic UC from the mesenchymal tumors and squamous cell carcinoma.\[^{7,9}\]

The present case was diagnosed with metastasis from UC as he had an established history of recurrent UC and the cytological examination revealed uniform cells that form multi-layered papillary fragments and syncytial configurations, occasional bipolar cells and CCs. Moreover, the fact that cells forming papillae were observed in the cytology specimen despite total absence of a papillary configuration in the neoplasm observed in the resection material that can be recorded as another interesting characteristic of the present case.

### Conclusion

In conclusion, lung metastasis from low-grade Ta UCs of the bladder is a rare entity and the presence of multi-layered papillary fragments, CCs, uniform cells with eccentric nuclei and occasional intracytoplasmic vacuoles are the main cytopathological features that would contribute to the diagnosis of UC, combined with clinical history.

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