

# SYNCHRONOUS INVASIVE UROTHELIAL CELL CARCINOMA OF THE BLADDER WITH CHRONIC MYELOID LEUKAEMIA – A CASE REPORT

Syakri Syahrir<sup>\*1</sup>, Muhammad Asykar Palinrunji<sup>\*</sup>, Prihantono Prihantono<sup>\*\*</sup> and Muhammad Faruk<sup>\*\*</sup>

<sup>\*</sup>Division of Urology, Department of Surgery, Faculty of Medicine, Hasanudin University; Hasanuddin University Hospital, Makassar, Indonesia., <sup>\*\*</sup>Department of Surgery, Faculty of Medicine, Hasanudin University; Hasanuddin University Hospital, Makassar, Indonesia.

**ABSTRACT** Incident of bladder carcinoma synchronous with CML was about 0.45%, and its treatment became a challenge. We reported a case of invasive urothelial cell carcinoma with chronic myeloid leukaemia (CML) in a 55-year-old man. The patient suffered painless gross hematuria from the first time. The patient complained of weight drop drastically and often accompanied by intermittent fever. The result of the biopsy examination of the spine was chronic phase CML, while the results of abdominal ultrasound and Multislice Computerized Tomography (MSCT) abdomen without contrast were a bladder mass. The patient underwent Transurethral Resection of a Bladder Tumor (TUR-BT) and therapy with imatinib. The pathology result showed that an Invasive Urothelial Cell Carcinoma. Our report concluded an uncommon case of Invasive Urothelial Cell Carcinoma and CML.

**KEYWORDS** synchronous, bladder carcinoma, chronic myeloid leukaemia

## INTRODUCTION

Bladder carcinoma was 2% of all malignancy types and was the second most common malignancy in the urogenital system after prostate carcinoma. The tumour was 3-4 times more common in men than women. In the industrial area, the incidence of the tumour increased sharply [1,2]

Early bladder carcinoma was a superficial tumour. The tumour gradually infiltrated into lamina propria, muscles, and perivesical fat, then spread directly to surrounding tissues. Also, the tumour could spread lymphogenously or hematogenous. Lymphogen spread to lymph nodes, perivesical, obturator, external iliac, and communal iliac. The more common hematogenous tumours were tumours which spread to liver, lungs and bones. Most of the bladder tumours ( $\pm$  90%) were urothelial cell carcinomas. These tumours were multifocal in the urinary tract, whose

epithelium consisted of urothelial cells such as in pielum, ureter, or posterior urethra. While the other types of bladder carcinoma were squamous cell carcinoma ( $\pm$  10%) and adenocarcinoma ( $\pm$  2%) [1,2]

Chronic Myeloid Leukemia (CML) was the first type of leukaemia discovered, and its pathogenesis was acknowledged [3]. In 1960 Nowell and Hungerford discovered chromosome abnormalities that suffered by CML patients, namely 22q - as partial loss of long arms of chromosome 22, which known as Philadelphia chromosome (Ph) [3].

Incidence of multiple primary cancers (MPC) such as bladder carcinoma and CML was very rare, about 0.52% [4]. The cancer was more common in the elderly, as increased incidence of malignancy as age increased [5]

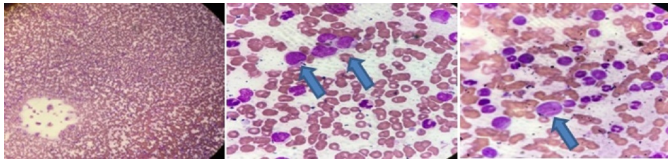
The purpose of this paper is to report a case of invasive urothelial cell carcinoma of the bladder Synchronous with chronic myeloid leukaemia.

## CASE REPORT

We reported a case of 55-year-old man complained of bleeding without pain experienced since  $\pm$  2 months ago. Bleeding was experienced when urinating continuously, since urinating started until the end. The patient was a chronic smoker, it was about 1-2 packs of tobacco per day. Job history was a farmer. Previous

Copyright © 2019 by the Bulgarian Association of Young Surgeons  
DOI:10.5455/ijsm.Synchronous-invasive-urothelial-cell-carcinoma  
First Received: November 24, 2018  
Accepted: July 15, 2019  
Manuscript Associate Editor: Ivan Inkov (BG)

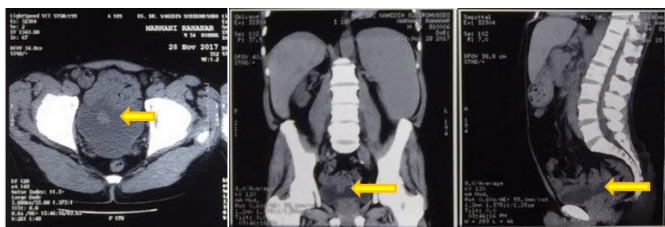
<sup>1</sup>Department of Surgery, Hasanuddin University, Makassar, Indonesia; E-mail: faroex8283@gmail.com



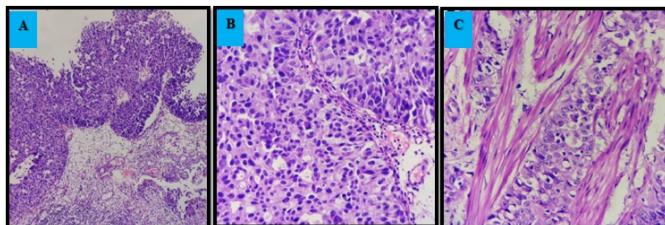
**Fig.1.** Bone Myeloid Chronic Bone Marrow Aspiration (10x enlargement). Bone Marrow Aspiration: Hypercellular with predominant myeloblast at 100x microscopic enlargement (blue arrow).



**Fig.2.** Abdomen ultrasound appeared mass on a jar (arrow).



**Fig.3.** Multi-Slice Computed Tomography Abdomen without Contrast Axial pieces appeared mass on the jar (arrow). Abdomen without Contrast Coronal cut appeared mass on the superior wall of the bladder (arrow). Abdomen without Contrast Sagittal pieces of mass on the superior wall of the bladder (arrow).



**Fig.4.** (A) Tumor histopathology of colouration of HE 100x. (B) Staining of HE 400x (C) Bladder tumours invaded connective and muscle tissues (HE, 400x staining). HE: Hematoxyline Eosin

treatment was in Makassar Hospital with complained of weight loss drastically, fever and a spinal cord examination, then the result of examination was leukaemia. Currently, the patient took a single dose of Imatinib drug 100 mg since 6 months ago.

In the examination, it was found that vital signs were within normal limits, and urological status was also within normal limits. On the digital rectal examination, the prostate condition was normal. Examination of Bone Marrow aspiration obtained was Chronic Phase Myeloid Leukemia (Figure 1). In addition, laboratory examination of Hemoglobin was 17.6 g/dL, leukocytes 29,000 mm<sup>3</sup>, platelets 527,000 / mm<sup>3</sup>, Neutrophils 85%. While CEA (Carcinoembryonic Antigen) result was 1.61 ng/ml. Abdomen ultrasound examination showed a mass of 3.04 x 2.13 x 2.01 cm bladder (Figure 2). Examination of Abdomen Multi-slice Computerized Tomography (MSCT) without contrast on Vesica Urinaria Mass also showed the appearance of the bladder such as firm border, irregular edge, 2x2x28 cm in size on superior wall of the bladder (Figure 3). While the examination of Chest X-Ray showed no metastatic signs. Regarding laboratory examination, it was found that Hb was 11.4 g / dL, leukocytes were 40,900 mm<sup>3</sup>, platelets were 854,000/mm<sup>3</sup>, neutrophils was 95.8%. Preoperative diagnosis of the patient was suspected malignant bladder tumour and chronic myeloid leukaemia.

Then, Transurethral Resection of a Bladder Tumor (TUR-BT) and Staging Operations were carried out. During surgery, staging method conducted in tumour mass at posterior bladder mucosa and resected until the base of tumour, and then performed Anatomical Pathology.

After surgery, the results of anatomical pathology examination showed that the nests of malignant epithelial cells from transitional epithelium, atypic, pleomorphic, hyperchromatic and prominent nucleoli nuclei were densely arranged which infiltrated stroma surrounding connective tissues, there were lots of nucleus cells scattered among tumour masses (Figure 4). As a result, it was concluded that the tumour mass was Invasive urothelial cell carcinoma. The diagnosis after surgery was Synchronous bladder Urothelial Cell Carcinoma (T2N0M0) and Chronic Myeloid Leukemia (CML).

After surgery, the patient did not make a routine visit to the hospital, so it was difficult to observe further for chemotherapy and radical cystectomy accompanied by lymphadenectomy of lymph nodes.

## DISCUSSION

We reported a patient who suffered double malignancies, namely Chronic Myeloid Leukemia and Urothelial Cell Carcinoma of the bladder, within 5 months. There were several predispositions and causative factors for each malignancy. However, the only one leading cause of this patient was a heavy smoker ( $\pm$  360 packs per year). There were no other predisposing factors or a family history of illness that might contribute to the development of this dual malignancies. Therefore, the presence of bladder cancer and CML was a rare event.

Histologically, bladder cancer was divided into urothelial, squamous and adenocarcinoma (or mixed, as a result of metaplasia in transitional cell carcinoma [TCC])[6]. More than 90% were from urothelial cells [6]. The cigarette was the main etiological factor (40% of cancers) [6]. Exposure to a urothelial carcinogen in the workplace was common [6]. The bladder cancer-caused by chemicals was discovered firstly by Rehn in 1895 when he recorded a series of tumours in workers at aniline dye factories [6]. Some examples of carcinogenic substances were benzidine

and chlornaphazine. Some workers were associated with increased risks of bladder cancer such as textile workers, shoe manufacturers, capster barber and chemical plants workers [6].

The phenomenon of several primary malignant neoplasms in the same patient was first described by Billroth et al., in the late 19th century. Since that time, many cases of double or triple primary malignant neoplasms had been reported in the literature. Incidence of bladder cancer transitional cell carcinoma (TCC) and CML was high in the elderly group. However, synchronous different urological and malignant in the patient was rare, and it was a challenge, as it was due to treatment difficulties [7]

Synchronous cancer was defined as the occurrence of 2 or more tumours in less than 6 months [5,8]. Certain organs, such as digestive tracts, skin, liver and lungs, appeared to be frequent predilections for synchronous epithelial and hematopoietic cancers [5]. While metachronous type was diagnosed at intervals of more than six months [5,8]. Various kinds of chemicals, including tobacco, aniline, benzidine, amino-aromatic and rubber dyes and infectious agents had been reported to be main causes of bladder cancer. Some etiologies of primary malignant tumours were very complex as included, such as environmental factors, genetic disorders, immunological disorders, previous treatment, sex and hormonal factors. Other tumours in cancer patient could be a metastasis from primary cancer or other malignancies. A cancer patient should be carefully examined to rule out of the possibility of metachronous cancer (successively) or synchronous (simultaneous) malignancy. A high level of suspicion was necessary to detect synchronous malignancies [5].

Synchronous cancer was a multiple primary cancer (MPC) was established or diagnosed to be distinguished from metastatic lesions. This required different histological features. If histology was similar, it is shown that the tumour appeared from a separate or different place. In this research reported that 51% of synchronous tumours had similar histological features and 49% with different histological features. Another type of MPC incidence was around 0.5 - 1% per year [9] Metacronus cancer was two or more primary cancers that took place at different times (more than 6 months from first cancer [9]. The interval period between the two cancers onset could be varied from 6 months to 30 years [9]. The overall incidence of MPC was 0.83% [9]. Most patients were men [9]. The most common diagnoses of MPC were laryngeal cancer and lung cancer and followed by cancer of lips and larynx [9]. The most common location of synchronous and metachronous in women patient was adenocarcinoma mammae while in the male patient was prostate cancer (21%), lung (14%), colon and rectum (14%), and oesophagus (9%)[9].

A common definition of multiple primary malignancies, according to Warren and Gates, stated that each tumour presented as a definite description of malignancy, each of them had to be different. Therefore, the possibility of other metastasis had to be excluded [8,9] Literature revealed 3 cases of synchronous cancer with CML. The average duration of first cancer to the second cancer was more than 6 months [12].

A unique case was found in the synchronous case involved five primary cancers with different histologies as Weingartner et al. (1995) reported malignancies from colon, kidney, prostate and bladder. The bladder was affected by two different tumours, such as TCC and histiocytoma fibrous cancer. [18]. While Honk et al. (2001) reported a 63-year-old man with contralateral kidney cancer that coincided with renal TCC (left) and RCC (right).

Although the results of cancer treatment and better survival rates had been proven, the incidence of a second primary cancer increased [19].

Tashiro et al. (1999) analyzed multiple cancer conditions observed bladder cancer in hospitals [21]. For 21 years, researchers treated 969 patients (828 men and 141 women) with primary bladder cancer. The analysis revealed that of 969 cases with bladder cancer, 81 patients (8.36%) had multiple cancers included 6 patients (0.61%) with three cancers. While the incidence of cancer-based on sex, it found that 70 men (8.45%) and 11 women (7.80%) had multiple cancers. While the incidence based on organ locations were 25 cases (2.57%) in the prostate, 23 cases (2.37%) in stomach, 20 cases (2.06%) in the breast, 14 cases (1.44%) in the colon and rectum [21]. Also, incidence based on the period of diagnosis, it found that 28 cases (34.6%) were diagnosed before, 28 cases (34.6%) simultaneously and 31 cases (38.3%) were secondary [21]. Therefore, the prognosis of multiple cancer patients with bladder cancer was poor compared with single bladder cancer patient. [20]

Helbig G. et al. reported that 221 CML patients treated with IM, 8 patients had SM (3.6%), and only 1 patient was synchronous with urothelial carcinoma. [22]. While Guilhot F. et al. in the literature mentioned 189 patients with CML treated with IM, 6 suffered from SM, with 3 people with prostate adenocarcinoma, 1 colon adenocarcinoma, 1 person with squamous cell carcinoma and 1 person with invasive urothelial cell carcinoma [4].

While in this research, Wahidin Sudirohusodo Hospital performed bladder resection transurethral for bladder cancer and had the administration of imatinib drugs since 6 months ago. However, the researcher did not conduct radical cystectomy with lymphectomy in pelvic lymph node as standard therapy for pT2 - pT3 stage malignant tumours without signs of metastasis. The researcher also did not perform neoadjuvant chemotherapy combined with cisplatin, methotrexate, doxorubicin and vinblastine (M-VAC) before radical cystectomy which was proven to improve patient survival rates, as patients refuse radical cystectomy and neoadjuvant chemotherapy for the urothelial cell carcinoma.

The prognosis in this patient with multiple such malignancies affected by aggressive tumours and this case depend on the bladder cancer type (T2N0M0).

## CONCLUSION

We reported a rare case of Urothelial Cell Carcinoma, which was found to be synchronous with CML. Regarding our knowledge, this case report was the first references, as Urothelial Cell Carcinoma was found to be synchronous Carcinoma with CML.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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