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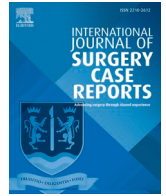
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Case report

Ureteral small cell neuroendocrine carcinoma: A case report and short review

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ABSTRACT

Introduction and importance: Primary small cell neuroendocrine carcinoma (SCNEC) in the urinary tract represents less than 0.5 % of urinary tract cancers, and bladder or prostate are the most common sites. Early diagnosis and treatment of ureteral SCNECs are challenging due to nonspecific clinical symptoms and radiographic findings. **Case presentation:** Here, we described a diagnostic and therapeutic challenge of a 56-year-old male with recurrent right flank pain that did not relieve with analgesics alone. The patient underwent several non-invasive to invasive procedures revealing nonspecific inflammation pathology of the ureter that later developed into protruded papillary mucosa resembling polypoid cystitis. Later, an abdominal multi-slice computed tomography examination suggested a malignant mass and was confirmed as SCNEC from the pathological analysis. After several successful chemotherapy cycles and surgical procedures, cancer reoccurred, and the patient's general condition deteriorated. He passed away a year after a radical cystoprostatectomy and nephroureterectomy on his right side.

Clinical discussions: The occurrence of primary SCNEC is a highly uncommon phenomenon. As SCNEC arises from pluripotent stem cells that have differentiated into neuroendocrine cells, some patients may exhibit paraneoplastic syndrome. The patient's prognosis of this tumor is poor, even for patients in the earliest phases, because SCNEC is characterized by highly aggressive local invasion and distant metastases.

Conclusions: This case highlights the importance of accurate early diagnosis and treatment of recurrent flank pain and considering the possibility of a malignant tumor as the cause of obstruction.

1. Introduction and importance

Small cell neuroendocrine carcinoma (SCNEC) as a primary tumor is uncommon in extrapulmonary organs but have reported in numerous sites, including gastrointestinal tracts, uterine cervix, kidney, urinary bladder, and prostate gland [1]. As an exceedingly uncommon urinary tract disease, it represents under 0.5 % of urinary tract cancers. The most common sites of SCNEC in the urinary tract are the bladder and prostate, whereas ureter involvement is rare. This tumor exhibits aggressive biological behavior. The prognosis for most primary ureteral SCNECs is bleak, with most patients dying within a year [2]. Early diagnosis and treatment of ureteral SCNECs are challenging due to nonspecific clinical symptoms and radiographic findings [3]. With this, we described a 56-year-old male with recurrent flank pain and found with a SCNEC of the ureter. This study aim to describe a diagnosis and management from

patient with SNEC. Informed consent has been received for this study. Ethical approval for this study (Ethical Committee N° 2223/129/4/VI/2023) was provided by the Ethical Committee from author institution, Surabaya, Indonesia on 13 June 2023. We followed the surgical case report (SCARE) checklist in writing this article [4].

2. Case report

A 56-year-old male was referred by a general urologist for recurrent right flank pain. He complained of flank pain for three months before seeing a general urologist. The urinalysis and laboratory examination within normal limit. Initial intravenous pyelography (IVP) revealed right renal hydronephrosis due to distal ureter obstruction. Abdominal CT-Scan was not performed due to economical constraint. The urologist performed a right ureteroscopy (URS). However, the procedure failed

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because the ureteroscope could not enter the ureter because of appeared to be solid mass blocking the ureteral orifice. The patient then referred to the hospital where the authors work.

The physical examination revealed right flank pain. Armed with data from the previous hospital, the URS was repeated on the right ureter. A papillary mass was found along the distal to medial ureter. A biopsy of the papillary mass mucosa was performed and the placement of a double J (DJ) stent was successful. The result of the pathology examination revealed polypoid cystitis, and no signs of malignancy were found. The DJ stent was placed for three months, and the patient had no further symptoms. After three months the DJ stent was removed, and the patient was recommended to return for a follow-up examination three months after the removal of the DJ stent. However, the patient experienced pain, two weeks after the DJ stent was removed. An abdominal multislice computerized tomography (MSCT) examination with contrast was performed. The results showed hydronephrosis and hydroureter with a lobulated enhancing mass on the posteroinferior bladder wall with extension to the perivesical layer and infiltrating the right ureterovesical junction causing obstruction, suggesting a malignant mass (Fig. 1). Chest radiographs were taken, and no primary or metastatic lung lesions were found. Subsequently, transurethral resection of the mass was then performed and the resected mass was send to pathologist for further examination. The pathology results were oval nuclear, pleomorphic, hyperchromatic, scant cytoplasm cells arranged in trabecular pattern, rosette pattern, moulding feature, and muscle tissue invasion (Hematoxylin and eosin (HE) stain on 200× magnification). The tumor cells exhibited cytoplasmic positivity for synaptophysin, cytokeratin and neuro specific enolase (NSE) Antibody on 400× magnification (Fig. 2). Chemotherapy with carboplatin and etoposide was administered for three cycles. After the third cycle of chemotherapy, re-evaluation of the tumor with an abdominal CT scan found the tumor had shrunk (Fig. 3). After the evaluation cystoprostatectomy, right nephroureterectomy and ileal conduit diversion was performed. The right kidney, ureter, prostate gland and bladder was removed (Fig. 4). Chemotherapy was continued

after the surgery until completion as scheduled. Six months after surgery, evaluation with abdominal CT scan found no recidive mass. Twelve months after the surgery, the patient complained of abdominal pain and difficulty defecating. After referring to digestive consultant it was concluded that there was a recurrence of the mass in the ileocecal junction area. As the patient's condition deteriorated, an ileostomy was performed. The patient's general condition did not improve and passed away ten days into treatment or one year post radical cystoprostatectomy.

3. Clinical discussion

In this study, we describe a case in diagnosing and managing a patient with SCNEC. Chemotherapy reduced the tumor size after the third cycle. Recidive mass after chemotherapy and surgery suggests incomplete tumor eradication. The patient's condition worsened despite different treatment modalities, resulting in a poor outcome.

The occurrence of primary SCNEC is a highly uncommon phenomenon, with a documented total of fewer than 50 cases since its initial identification in 1986. The scarcity of cases has resulted in limited knowledge regarding the clinicopathologic features and prognosis of affected individuals, with histological analysis as the primary diagnostic tool [3].

Hematuria, gross or microscopic, and flank pain are frequent manifestations of these tumors. Ureteral NECs are comparable to other urothelial carcinomas, whereas a few patients manifest the syndrome of inappropriate antidiuretic hormone secretion [1,3]. As SCNEC arises from pluripotent stem cells that have differentiated into neuroendocrine cells, some patients may exhibit paraneoplastic syndrome [5–7]. When these symptoms manifest, it is possible that the disease has reached an advanced or extensive stage. The patient's prognosis of this tumor is poor, even for patients in the earliest phases, because SCNEC is characterized by highly aggressive local invasion and distant metastases. Lymph nodes and bone are the most common sites for metastasis. However, it is essential to rule out primary lung tumors that have metastasize. Chest X-rays or CT scans may be performed to rule out pulmonary malignancy. Seventeen months is the median overall survival rate, while the 1-year survival rate is 51.9 % and 30 % for the 3-year survival rate. [8–10]

The diagnosis of SNEC mostly relies on histology. The important component for diagnosing SNEC are structure for neuroendocrine granules and positive immunohistochemistry for synaptophysin and neuron-specific enolase [9]. Other method that helps on diagnosing SCNEC can be made based on the examination of serum and urinary catecholamines and metanephrines, abdominal CT-Scan or MRI. Since catecholamines (norepinephrin, epinephrin, and dopamine) are secreted by neuroendocrine tumors, elevated urine or serum catecholamine levels are associated with SCNEC. Traditional signs of excess catecholamines in the body include headache, palpitations, perspiration, and fluctuating blood pressure [11]. The most sensible blood and urinary endocrine test was reported to be urinary metanephrines [12]. Urinary catecholamines or metanephrines can be a screening for neuroendocrine tumors including SCNEC as it is a non-invasive method. Catecholamines or metanephrines measurement was not performed in our patient due to the biopsy was already clear in showing SCNEC pathology.

To the best of our knowledge, no well-established standard treatment techniques or agreement for ureteral SNEC exist Decision-making in patient management is mainly based on prior published case reports [3]. The most commonly used treatment for SCNEC is the combination of surgery (cystoprostatectomy, nephroureterectomy), chemotherapy, and radiation. According to several research, cisplatin-based chemotherapy seems to have a superior prognosis and survival rate [13]. For additional bladder invasion, several authors advise platinum-containing and etoposide regimens [14]. Ahsaini et al. reported the successful treatment of urinary tract SCNEC with neoadjuvant chemotherapy (ifosfamide/doxorubicin and etoposide/cisplatin). The patient was still disease-free

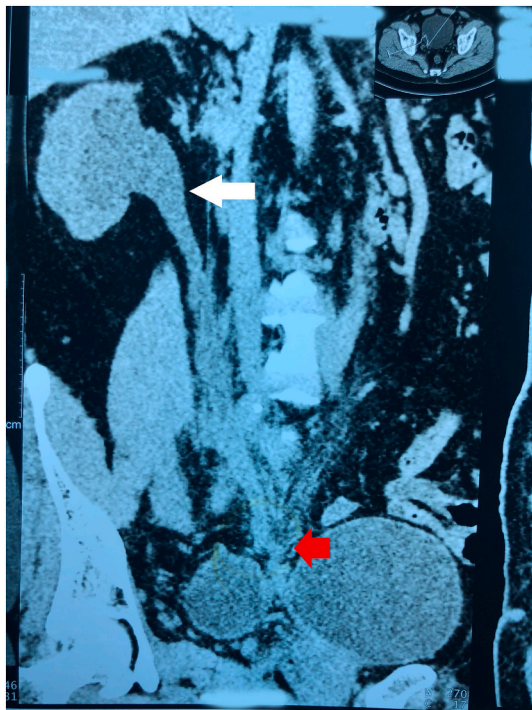


Fig. 1. Abdominal MSCT. (White Arrow) Dilated proximal ureter and kidney suggesting hydronephrosis and hydroureter and (Red Arrow) Location of obstruction caused by the mass. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

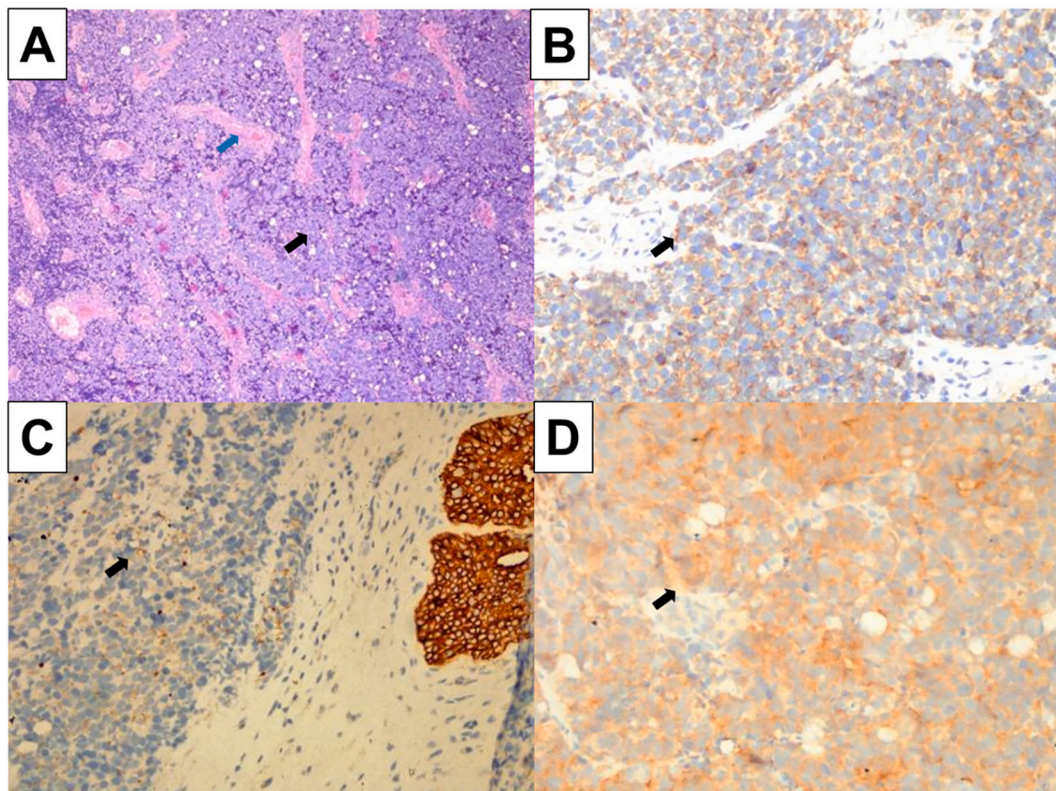


Fig. 2. Pathology of SCNEC. (A) Histopathological examination showing tumor growth consists of round to oval nuclear, pleomorphic, hyperchromatic, scant cytoplasm cells (black arrow) arranged in trabecular pattern, rosette pattern, moulding feature, and muscle tissue invasion (blue Arrow) (HE stain; magnification x 200). (B) Immunohistochemical examination using Synaptophysin antibody shows positive staining in tumor cells cytoplasm (Arrow) (magnification x 400). (C) Immunohistochemical examination using Cytokeratin antibody shows focally positive staining in tumor cells cytoplasm (magnification x 400). (D) Immunohistochemical examination using Neuro Specific Enolase (NSE) antibody shows positive staining in tumor cells cytoplasm (arrow) (magnification x 400). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

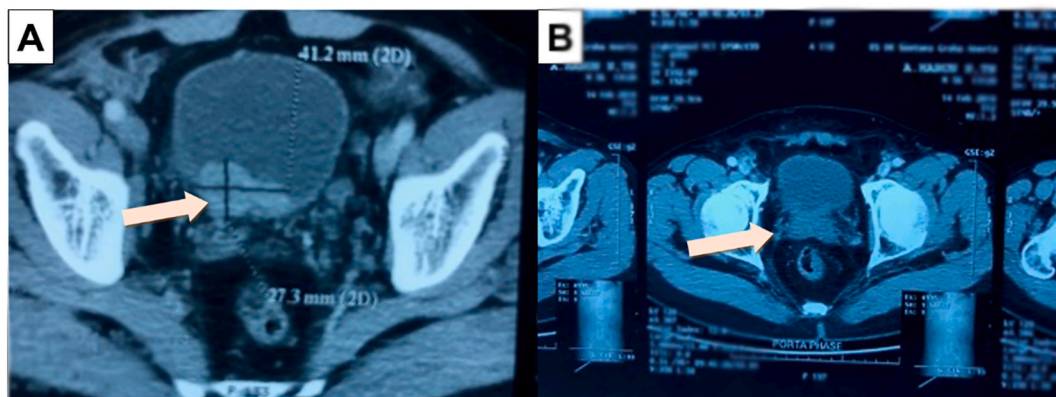


Fig. 3. Abdominal MSCT. (A) Tumor mass around the right ureter moiety prior to the chemotherapy and (B) after chemotherapy.

within two years of follow-up [15]. In another case report, the patient was managed with four cycles of neoadjuvant chemotherapy with cisplatin/etoposide. The patient was free of disease within 13 months follow-up [16].

This case report highlights the importance of a thorough evaluation for patients with recurrent flank pain and suspected urinary tract obstruction. This case emphasizes the need for continued monitoring and evaluation even after successful treatment of a urinary tract obstruction or cancer, as recurrence is possible. Early detection is crucial for better outcomes.

4. Conclusion

This study emphasizes the significance of timely and precise diagnosis for managing rare cases of primary SCNEC in the ureter. Although chemotherapy and surgery succeeded in initially decreasing the tumor size, the outcome was unfavorable due to reoccurrence of the tumor. Because SCNEC in the ureter is rare, little is known regarding its clinical, pathological, and prognostic characteristics. Currently, the most reliable method of diagnosis is histological examination. To prevent recurrence and enhance outcomes, performing a comprehensive assessment and follow-up of patients is important.

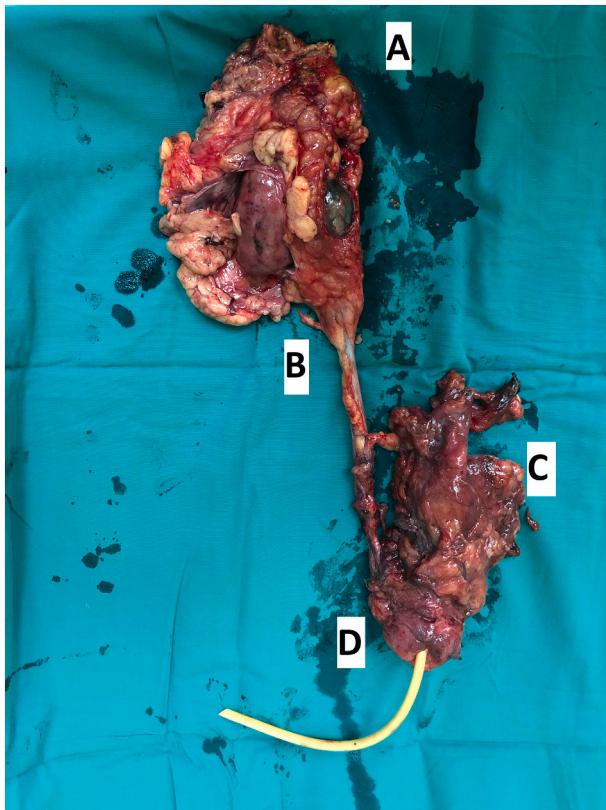


Fig. 4. Resected mass with the removal of (A) right kidney, (B) right ureter, (C) Part Bladder, (D) Prostate.

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Ethics statement

Ethical approval for this study (2223/129/4/VI/2023) was provided by the Ethical Committee Dr. Soetomo Hospital, Surabaya, Indonesia on 13 June 2023.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Credit authorship contribution statement

Wahjoe Djatisoesanto: conceptualization, data collection, validation, writing – original drafting, writing – review & editing, supervision.

Ida Bagus Gde Tirta Yoga Yatindra: data collection, writing – original drafting, writing – review & editing.

Anny Setijo Rahaju: data collection, writing – original drafting, writing – review & editing.

Registration of research studies

1. Name of the registry: Not required
2. Unique identifying number or registration ID: Not required
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Not required

Guarantor

Wahjoe Djatisoesanto.

Declaration of competing interest

None.

Acknowledgement

None declared.

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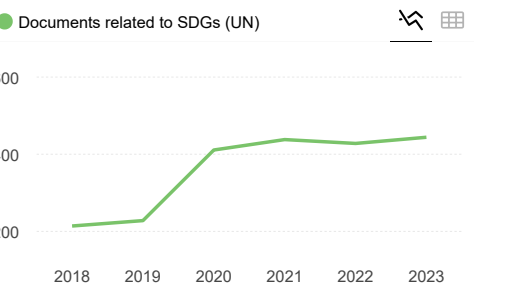
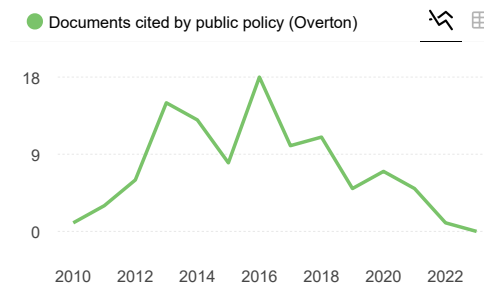
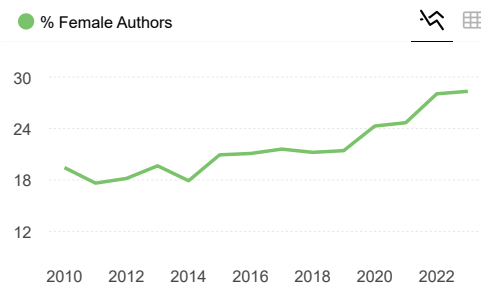
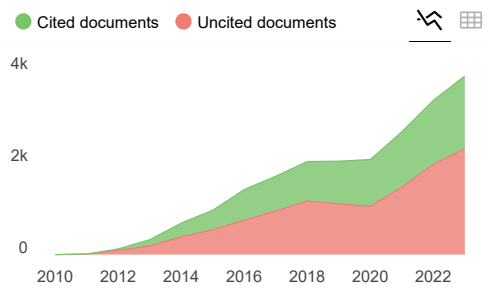
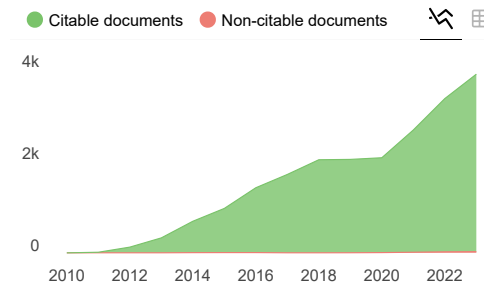
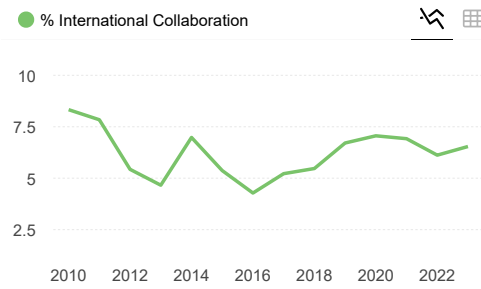
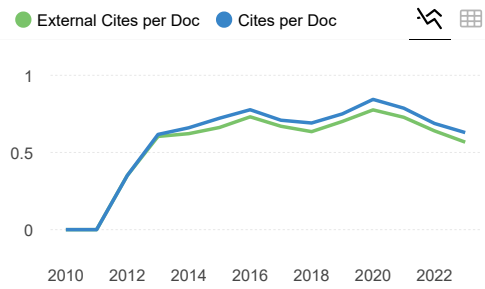
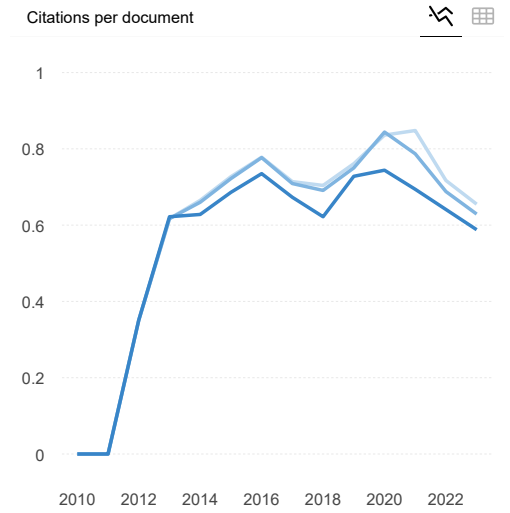
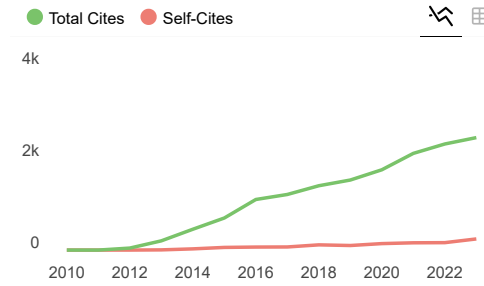
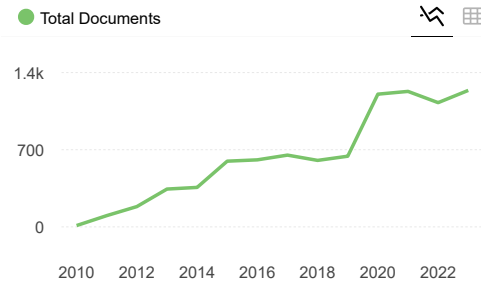
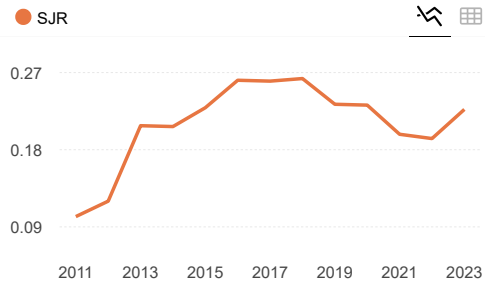
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