Respiratory Medicine Case Reports 53 (2025) 102166

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case Report

Klinefelter syndrome diagnosed at autopsy and small-cell lung carcinoma

Haruyasu Sakuranaka [a,*], Ryoma Tanaka [a,b], Yuji Yamakawa [a], Shiho Yamada [a,b], Komei Igei [a,b], Yasuo Asai [a,b]

[a] Respiratory Medicine, Tokyo Metropolitan Toshima Hospital, 33-1, Sakaecho, Itabashi-Ku, Tokyo, 173-0015, Japan
[b] Department of Internal Medicine, Division of Respiratory Medicine, Nihon University School of Medicine, 30-1, Oyaguchikamicho, Itabashi-Ku, Tokyo, 173-8601, Japan

ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Klinefelter syndrome
Autopsy
Lung cancer
Small-cell lung carcinoma
Fluorescence in situ hybridization

ABSTRACT

Klinefelter syndrome is characterized by endocrine abnormalities, gynecomastia, female-like body shape, and mild intellectual disability. However, the diagnosis of Klinefelter syndrome is often missed due to the lack of characteristic findings. Computed tomography revealed a mass in the left lung of a 66-year-old man. He was diagnosed with small-cell lung carcinoma. Chemotherapy was administered, but the disease progressed, eventually leading to death. No significant changes were observed in the external genitalia or breast, but the autopsy showed testicular atrophy. XXY cells were seen in fluorescence in situ hybridization, and Klinefelter syndrome was diagnosed. Although chemotherapy causes testicular atrophy, Klinefelter syndrome should be considered in cases of severe testicular atrophy.

1. Introduction

Klinefelter syndrome is characterized by endocrine abnormalities, gynecomastia, female-like body shape, and mild intellectual disability [1–3]. Klinefelter syndrome is often overlooked in the absence of physical or mental characteristics. The present case showed no significant physical or mental abnormalities, and Klinefelter syndrome was not diagnosed before death. However, pathological autopsy confirmed testicular atrophy, and the diagnosis of Klinefelter syndrome using fluorescence in situ hybridization (FISH). Because chemotherapy can cause testicular atrophy, we will discuss whether testicular atrophy was caused by Klinefelter syndrome or chemotherapy.

2. Case presentation

A 66-year-old man complaining of fatigue presented to a general practitioner. He had a 35-pack-year smoking history. Chest X-ray revealed a mass shadow in the left pulmonary hilar region (Fig. 1), and the patient was referred to our hospital. A computed tomography (CT) revealed a 50-mm diameter mass in the upper lobe of the left lung, along with enlarged mediastinal and left clavicular lymph nodes and a mass in the liver (Fig. 2). Small-cell lung carcinoma was diagnosed after bronchoscopic biopsy of the mass in the upper lobe of the left lung (Fig. 3). We diagnosed extensive-stage small-cell lung carcinoma.

* Corresponding author.
E-mail address: hal_amazon@yahoo.co.jp (H. Sakuranaka).

https://doi.org/10.1016/j.rmcr.2025.102166
Received 3 September 2024; Received in revised form 9 January 2025; Accepted 15 January 2025
Available online 17 January 2025

The patient was administered with carboplatin plus etoposide. After the second course, he could not walk unaided, and the size of the left lung mass had increased. Consequently, we provided supportive care because chemotherapy was ineffective.

He died 5 months after he visited our hospital. The pathological autopsy revealed small-cell carcinoma of the left lung, mediastinal invasion, pericardial sac invasion, and liver, medullary, and lymph node metastases, which were diagnosed as the cause of death. No significant changes were observed in the external genitalia or breast, but the testes were bilaterally atrophic and weighed 7.7 g after specimen preparation. Histologically, almost all of the ductus deferens showed vitrification, and the lumen had no cellular components. Leydig cells showed diffuse hyperplasia (Fig. 4). The presence of XXY cells was confirmed using FISH and biopsy of lung specimens (Fig. 5), and Klinefelter syndrome was diagnosed.

3. Discussion

Klinefelter syndrome was initially reported in 1942, and an excess of X chromosomes was found in 1959 [1,2]. It is characterized by endocrine abnormalities, gynecomastia, a female-like body shape, and mild intellectual disability [3]. The present case did not show significant physical or mental changes, and only testicular atrophy was observed physically, making the diagnosis of Klinefelter syndrome before death difficult.

Chemotherapy causes testicular atrophy. The degree of testicular atrophy depends on the chemotherapy drugs used, dosage, treatment duration, and patient age [4]. Alkylating agents, such as cyclophosphamide, cause long-lasting azoospermia, and platinum agents, such as cisplatin and carboplatin, may cause prolonged azoospermia [5,6]. Other chemotherapeutic agents used for lung cancer, such as etoposide, irinotecan, gemcitabine, amrubicin, vinorelbine, paclitaxel, docetaxel, tegafur, fluorouracil, and pemetrexed, often result in only temporary sperm loss [5,6]. The effects of tyrosine kinase inhibitors and monoclonal antibodies on spermatogenesis are unclear but are thought to be limited [5,6]. The combination of agents known to cause azoospermia does not result in testicular atrophy immediately after a limited number of treatments in elderly patients. A previous study reported that testicular weight was reduced by half after six cycles of cyclophosphamide-containing chemotherapy and radiation therapy in a group of patients with a mean age of 23 years and a mean followup of 6 years [7].

We used carboplatin plus etoposide in this case, but it was administered only twice. Compared with the average Japanese testicular weight (60–69 years: left testis, 12.89 $\pm$ 4.00 g; right testis, 13.86 $\pm$ 4.03 g) [8], the testicular weight in this case was less than half. Therefore, we investigated for other factors regarding testicular atrophy, and were able to diagnose Klinefelter syndrome.

Klinefelter syndrome has a high rate of malignancy, and endocrine and chromosomal abnormalities were thought to be the cause [3]. Breast cancer, non-Hodgkin lymphoma, and leukemia have significantly higher morbidity and mortality rates [3,9]. Conversely, prostate cancer has low morbidity and mortality [3,9]. These findings support an endocrine etiology for breast and prostate cancer in men. Hematopoietic malignancies may be associated with chromosomal abnormalities. Reports have shown a trend toward increased morbidity and mortality rates for lung cancer, although these rates are not significantly different [3,9]. Moreover, smoking rates are higher in individuals with Klinefelter syndrome than in the general population [10], which may be a contributing factor to the elevated morbidity and mortality rates of lung cancer. However, smoking-related cancers, including those of the mouth, pharynx, esophagus, pancreas, larynx, and bladder, generally have lower rates of morbidity and mortality [3,9]. Other factors besides smoking may contribute to the link between Klinefelter syndrome and lung cancer. The patient in this case was a heavy smoker, and smoking may have been involved in the development of small-cell lung cancer. Quitting smoking becomes even more crucial in preventing lung cancer in patients with Klinefelter syndrome.

4. Conclusion

The autopsy revealed Klinefelter syndrome, which had not been diagnosed before death. Notably, the diagnosis of Klinefelter syndrome can be missed in the absence of significant physical or mental changes. Although chemotherapy causes testicular atrophy,

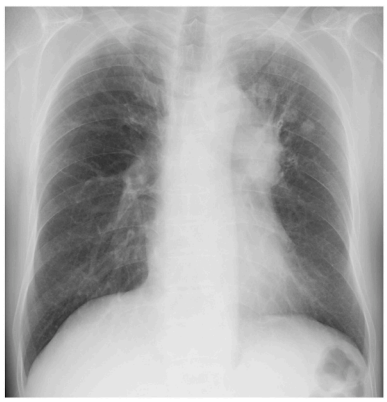

Fig. 1. Chest X-ray showing a mass shadow in the left pulmonary hilar region.

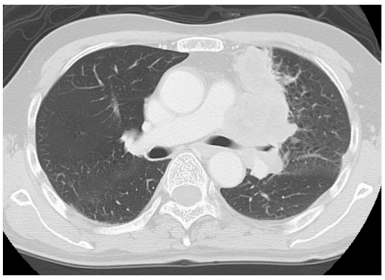

Fig. 2. Computed tomography (CT) showing a 50-mm diameter mass in the upper lobe of the left lung.

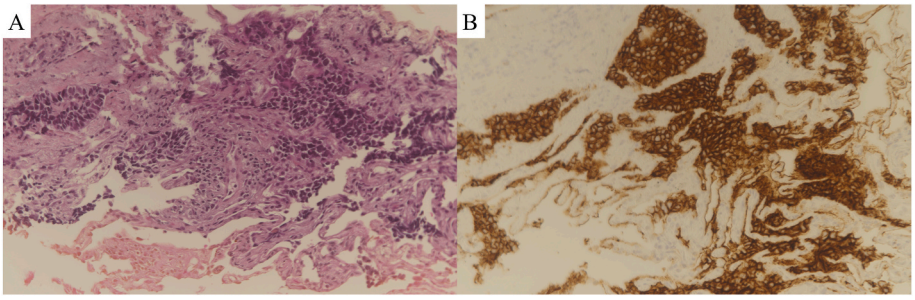

Fig. 3. (A) Histological results of the bronchoscopic biopsy (hematoxylin and eosin staining, magnification × 200) show small round carcinoma cells with enlarged nuclei infiltrate and proliferate. (B) The tumor cells are positive for CD56 (magnification × 200), indicating small-cell carcinoma.

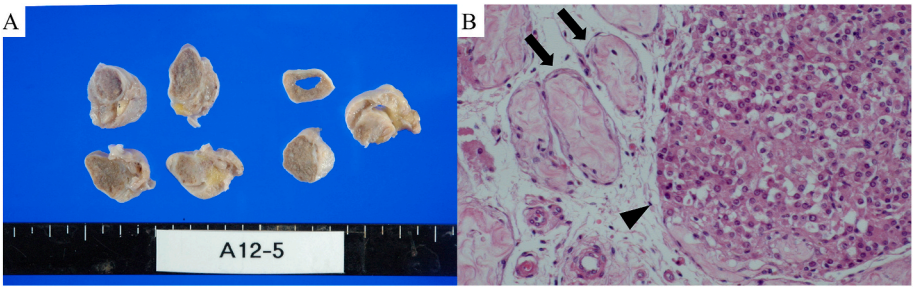

Fig. 4. (A) The testes are bilaterally atrophic and weigh 7.7 g after specimen preparation. (B) Histologically (magnification × 400), almost all of the ductus deferens showed vitrification, and the lumen had no cellular components (arrows). Diffuse hyperplasia of Leydig cells is observed (arrowhead).

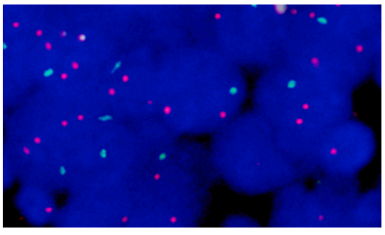

Fig. 5. Fluorescence in situ hybridization (FISH) with biopsy specimens from the lung. Red and green indicate chromosomes X and Y, respectively. The presence of XXY cells was confirmed.

Klinefelter syndrome should be considered in cases of severe testicular atrophy.

CRediT authorship contribution statement

Haruyasu Sakuranaka: Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization. **Ryoma Tanaka:** Writing – review & editing, Data curation. **Yuji Yamakawa:** Writing – review & editing, Data curation. **Shiho Yamada:** Writing – review & editing, Data curation. **Komei Igei:** Writing – review & editing, Data curation. **Yasuo Asai:** Writing – review & editing, Data curation.

Ethics approval and consent to participate

Ethics approval does not apply to case reports, and the patient was not a participant in the study.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Availability of data and materials

The data supporting this case report are available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used DeepL in order to improve language and readability. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to express our appreciation to Dr Shikofumi Tei for his constructive suggestions and continuous support.

Glossary

FISH	fluorescence in situ hybridization
CT	Computed tomography

References

[1] Jr HF. Klinefelter, Jr EC. Reifenstein, Jr F. Albright, Syndrome characterized by gynecomastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle-stimulating hormone, J. Clin. Endocrinol. Metab. 2 (1942) 615–627, https://doi.org/10.1210/jcem-2-11-615.
[2] P.A. Jacobs, J.A. Strong, A case of human intersexuality having a possible XXY sex-determining mechanism, Nature 183 (1959) 302–303, https://doi.org/10.1038/183302a0.
[3] A.J. Swerdlow, M.J. Schoemaker, C.D. Higgins, A.F. Wright, P.A. Jacobs, UK Clinical Cytogenetics Group, Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study, J. Natl. Cancer Inst. 97 (2005) 1204–1210, https://doi.org/10.1093/jnci/dji240.
[4] T.J. Kinsella, Effects of radiation therapy and chemotherapy on testicular function, Prog. Clin. Biol. Res. 302 (1989) 157–171.
[5] S.J. Lee, L.R. Schover, A.H. Partridge, P. Patrizio, W.H. Wallace, K. Hagerty, L.N. Beck, L.V. Brennan, K. Oktay, American Society of Clinical Oncology recommendations on fertility preservation in cancer patients, J. Clin. Oncol. 24 (2006) 2917–2931, https://doi.org/10.1200/JCO.2006.06.5888.
[6] A.W. Loren, P.B. Mangu, L.N. Beck, L. Brennan, A.J. Magdalinski, A.H. Partridge, G. Quinn, W.H. Wallace, K. Oktay, Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update, J. Clin. Oncol. 31 (2013) 2500–2510, https://doi.org/10.1200/JCO.2013.49.2678.
[7] B.S. Charak, R. Gupta, P. Mandrekar, N.A. Sheth, S.D. Banavali, T.K. Saikia, R. Gopal, K.A. Dinshaw, S.H. Advani, Testicular dysfunction after cyclophosphamide-vincristine-procarbazine-prednisolone chemotherapy for advanced Hodgkin's disease. A long-term follow-up study, Cancer 65 (1990) 1903–1906, https://doi.org/10.1002/1097-0142(19900501)65:9<1903::AID-CNCR2820650905>3.0.CO;2-%23.

[8] T. Tasaka, S. Hiraga, M. Kitamura, T. Iida, J. Kurokawa, M. Hida, T. Satoh, [First report on studies of normal testicular weight and size in the Japanese], Nihon Hinyokika Gakkai Zasshi 77 (1986) 1506–1510, https://doi.org/10.5980/jpnjurol1928.77.9_1506.
[9] H. Hasle, A. Mellemgaard, J. Nielsen, J. Hansen, Cancer incidence in men with Klinefelter syndrome, Br. J. Cancer 71 (1995) 416–420, https://doi.org/10.1038/bjc.1995.85.
[10] A. Skakkebæk, P.J. Moore, S. Chang, J. Fedder, C.H. Gravholt, Quality of life in men with Klinefelter syndrome: the impact of genotype, health, socioeconomics, and sexual function, Genet. Med. 20 (2018) 214–222, https://doi.org/10.1038/gim.2017.110.