



An Intriguing Case of Chemical Mimicry: Raised AFP Levels in NUT Carcinoma in Anterior Mediastinum

Manasi Chetan Mundada¹ Daphne Fonseca¹  Faiq Ahmed¹ Suseela Kodandpani¹ Nikhil Pathi²

¹ Department of Laboratory Medicine, Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad, India

² Department of Medical Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad, India

Address for correspondence Manasi Chetan Mundada, MD, DNB, Department of Laboratory Medicine, Basavatarakam Indo American Cancer Hospital and Research Institute, Rd No 10, Banjara Hills, Hyderabad 500 034, India (e-mail: manasicmundada@gmail.com).

Ind J Med Paediatr Oncol 2026;47:329–332.

Abstract

Nuclear protein of the testis (NUT) carcinoma (NC) is a rare and aggressive neoplasm that predominantly involves the thorax and the head and neck region. The hallmark of this neoplasm is its non-descript, poorly differentiated morphology, immunohistochemical mimicry and chemoresistance, leading to an almost invariably fatal outcome. A 47-year-old gentleman presented with a history of hoarseness of voice for one month, along with a recent development of shortness of breath. A CT scan showed the presence of mass in the anterior mediastinum with impending superior vena cava syndrome. Serum alpha-fetoprotein levels (AFP) and lactate dehydrogenase (LDH) were raised, done on clinical suspicion of a germ cell tumor. On morphology, the tumor showed a poorly differentiated phenotype with occasional foci resembling abrupt keratinization. Immunohistochemistry was positive for AE1/3, p40 and p63; however, markers for germ cell tumor, lymphoma, and small cell carcinoma were negative. The diagnosis of NC was clinched by NUT immunohistochemistry. NC presenting with raised AFP levels is an exceptional clinical scenario. To the best of our knowledge, this is the first case to be reported from India.

Keywords

- NUT carcinoma
- raised AFP
- mediastinum
- abrupt keratinization

Introduction

Nuclear protein of the testis (NUT) carcinoma (NC) is a rare and aggressive neoplasm involving predominantly the thorax and head and neck region. The hallmark of this neoplasm is the non-descript, poorly differentiated morphology, immunohistochemical mimicry, and chemoresistance, leading to an almost always fatal outcome. Earlier this entity was also known as midline NUT carcinoma due to its predilection for midline location in the body. It is commonly described in young adults, though it shows a varied age predisposition.

Case Report

A 47-year-old gentleman presented with a history of hoarseness of voice for 1 month and recent development of shortness of breath. Serum AFP (3,400 IU/mL, normal range 0–7 IU/mL) and LDH (663 U/L, normal range 120–246 U/L) were raised and were ordered on clinical suspicion of a germ cell tumor. Beta HCG levels were normal. Physical examination revealed fullness in the right supraclavicular fossa. A CT scan showed the presence of mass in the anterior mediastinum with impending superior vena cava syndrome. A large mass was noted in the anterior and superior mediastinum, mea-

article published online
May 20, 2026

DOI <https://doi.org/10.1055/s-0046-1822840>.
ISSN 0971-5851.

© 2026. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

Thieme Medical and Scientific Publishers Private Limited, A-13A, Graphix Tower 1, 6th floor, Sector 62, Noida 201309, Uttar Pradesh, India

suring $58 \times 54 \times 77$ mm. A Trucut biopsy was done. H&E-stained sections showed extensive areas of necrosis. The neoplasm was arranged in nests and sheets, with large monomorphic cells having a high N/C ratio, vesicular nuclei, and conspicuous nucleoli. Rare foci resembling abrupt keratinization were noted. Fibrous areas between the tumor nests showed the presence of inflammatory cells.

With the history of raised serum germ cell markers, superior vena cava syndrome and a poorly differentiated phenotype on morphology, a broad immunohistochemistry (IHC) panel consisting of AE1/3, LCA, CD56, synaptophysin, p40, p63, SALL4, CD117, CD5, CD30, and OCT3/4 was ordered.

Immunohistochemistry was diffusely positive for AE1/3, p40, and p63; however markers for germ cell tumor, lymphoma, thymic carcinoma, and small cell carcinoma were negative. A pathological diagnosis of poorly differentiated squamous cell carcinoma and a clinical diagnosis of germ cell tumor were included. This diagnostic conundrum was solved by NUT immunohistochemistry, which demonstrated the speckled nuclear staining pattern. The case was discussed in multidisciplinary tumor board, Chemotherapy with Etoposide and Platinum based drugs could be offered to the patient. Prognosis was explained to the patient, he refused treatment at the present center.

Discussion

NC is a rare malignancy, the incidence of which is not described. The most common site of involvement is the

thorax (50%), followed by the head and neck (40%). Other than midline sites, locations such as bone and soft tissue, bladder, orbit, salivary gland, kidney, brain, nasal septum, etc. have been described in the literature.¹⁻³ The neoplasm is common in young adults with the median age of presentation varying between 22 and 68 years, is frequently seen in midline locations and has no specific association with smoking.⁴ In normal cell, NUT is responsible for differentiation and is found in post-meiotic spermatogones. In tumors, the presence of the classic translocation (15, 19), causes juxtaposition of BRD4-NUTM1, and the chimeric protein so formed interferes with the balance of acetylation/deacetylation in the cells. The result is increased expression of transcription factors like MYC, TP63, SOX2, which drive cell proliferation and arrest differentiation.⁴ Other less common partners in translocation with NUTM1 described are BRD3, NSD3, ZNF532, and ZNF592.^{5,6}

Morphological clues to suspect this entity would be the presence of poorly differentiated monomorphic cell morphology in the thoracic/midline region, absence of an in situ component, abrupt keratinization (juxta positioning of poorly differentiated cells with differentiated keratinized squamous islands), extensive necrosis, and intratumoral neutrophils,^{1,7} few of these features were seen in the present case (► Fig. 1)

In the absence of the following features, the common differential diagnoses include thymic carcinoma, small cell carcinoma, germ cell tumor, non-Hodgkin lymphoma, and Ewings's sarcoma, in light of the clinical, morphological, and biochemical parameters.^{8,9}

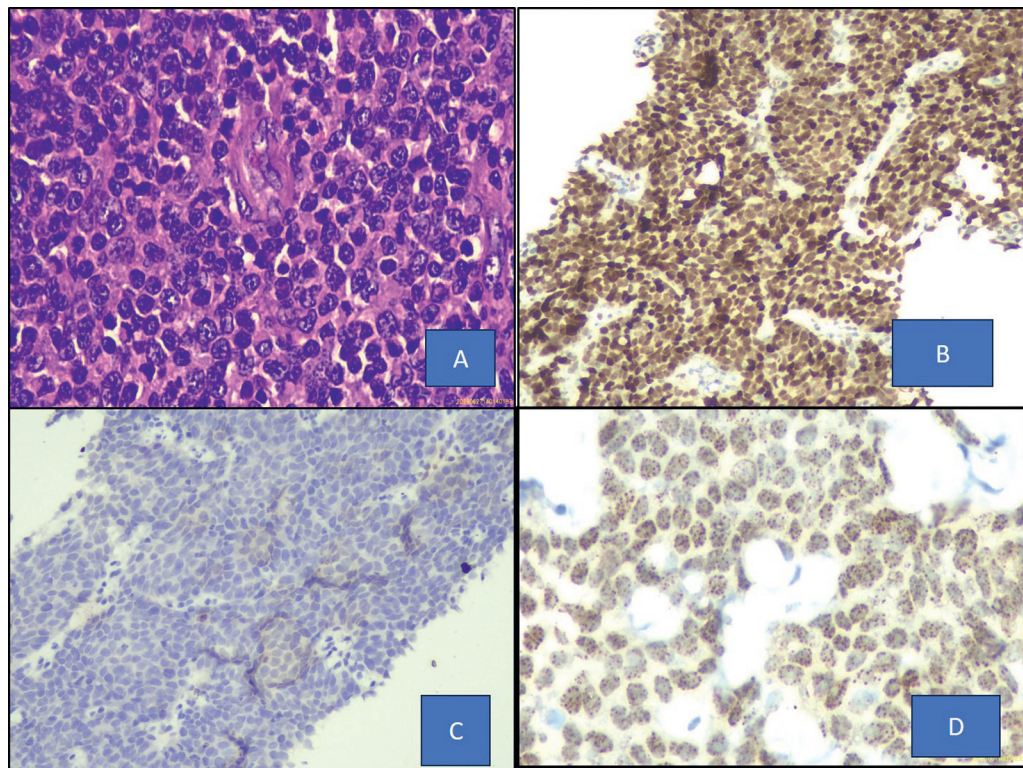


Fig. 1 (A) H&E stained slides showing sheets of monomorphic cells, showing high NC ratio and scant cytoplasm 400x. (B) Immunohistochemistry stain for p63, diffuse positive staining noted 400x. (C) Immunohistochemistry SALL4 stain: negative expression 400x. (D) NUT immunostain showing speckled staining pattern 400x. H&E, hematoxylin and eosin; NC, nuclear protein of the testis carcinoma; NUT, nuclear protein of the testis.

Table 1 Cases reported in literature of NUT carcinoma presenting with raised AFP levels

Sr. no.	Publication	Age/gender	Site	Metastasis	IHC profile	AFP	LDH	Follow-up
1.	Zhu et al (2011) ¹²	42/M	Lung	NA	Vimentin,EMA,CD99,CD138, p63	545	NA	Tumor progressed and lost to follow up
2	Ball et al (2012) ¹⁶	19//F	Thorax	Pelvic mass	P63	326	1,982	Succumbed to disease in 5 mo
3	Parikh et al (2013) ¹⁰	36/M	Hilar mass	Thoracic and abdomen aorta, diaphragm and subcutaneous, pleura, trachea	AE1/AE3, CD138,OSCAR, CAM5.2, TTF1,CD56	62	NA	Succumbed to disease in 15 d
4	Raza et al (2015) ¹⁴	36/M	Mediastinum/lung	Cervical lymph nodes	P63,ck5/6, CK7synaptophysin, CD99, CD138	1,742	761	Succumbed to disease in 10 mo
5	Harada et al (2016) ⁵	28/M	Mediastinum	Bones	AE1/3,p40,p63	163.8	667	Succumbed to disease 4.5 mo
6	D'Ambrosio et al (2017) ⁷	22/M	mediastinum-superior vena cava syndrome	Lymph nodes, bones	AE1/3, TTF1, synaptophysin, chromogranin, CD34EMA, CK7	765	14,468	Disease progression at 2.5 mo
7	Oualla et al (2018) ⁹	23/M	Mediastinopulmonary mass	NA	AE1/AE3, P63	350	2,500	Succumbed to disease in 1 mo
8	Murano et al (2021) ⁸	25/M	Mediastinum	Vertebrae, b// Femur	Vimentin, S-100, Melan A, AE1/3,CD99,EMA	74.6	564	Succumbed to disease in 73 d
9	Gasljevic et al (2021) ¹¹	47/M	Mediastinum/lung	Lymph nodes, bones, subcutaneous tissue	AE1/3,MNF11,EMA,p63, TTF1,LCA,CK7,CK5, CD138, CK18, AFP	6,389	NA	Succumbed to disease in less than 2 mo
10	Lai et al (2024) ¹⁵	-/F	Thorax/lung	Lung, liver, vertebra placenta	AE1/3, p40,p63,CK5/6, synaptophysin,S100, TTF1, INSM1, AFP	18,757	NA	Pembrolizumab with radiotherapy, succumbed to disease in 50 d
11	Matsuura et al (2024) ²	35/M	Lung	Lymph node, bone	AFP,CD56, SALL4, Synaptophysin	3,335	415	Succumbed to disease in 6 mo
12	Present case	47/M	mediastinum	None	AE1/3,p40,p63	3,400	663	Refused treatment

Abbreviations: AFP, alpha-fetoprotein levels; IHC, immunohistochemistry; LDH, lactate dehydrogenase; NA, not available.

Immunohistochemistry findings are promiscuous with several authors describing expression of AE1/3, p40, p63, and synaptophysin commonly.^{5,9–11} Other less commonly described expressions include LCA,¹¹ CD99,^{8,12} CD34,⁷ EMA,^{8,11,12} CD138,^{8,10,11} AFP, and SALL4.² The diagnostic surrogate marker for the translocation is NUT by IHC (clone:C52B1) or its demonstration by molecular modalities (FISH/RT-PCR/NGS). IHC for NUT is a cheap and time-efficient means of diagnosis with good sensitivity and specificity.¹

In the present case, morphology with immunohistochemistry hinted toward squamous cell differentiation, and markers were done to rule out thymic squamous cell carcinoma. IHC with NUT steered the diagnosis toward NC. However, this diagnosis failed to explain the high AFP levels observed in the patient. Raised AFP levels have been described in many tumors such as hepatocellular carcinoma, non-seminomatous germ cell tumor, gastric carcinoma, colorectal carcinoma with enteroblastic differentiation, Xp11 translocated renal cell carcinoma, etc.¹³; however none of them could explain this clinico-pathological conundrum.

A literature review described the presence of raised AFP in few cases of NC. This finding, though rare, has been described in around 11 cases in world literature. Clinico-morphological details of these are described in ►Table 1. Apart from the raised AFP levels, almost all of these patients presented with raised LDH levels, metastatic disease, and a dismal outcome in all cases. AFP levels seem to correlate with disease progression, similarly LDH levels also correlate with disease burden.

The reason for the aberrant AFP levels is not known, the hypothesis being that the cell of origin of these tumors is from primitive neural crest-derived cells.¹⁴ The utility of AFP can be in monitoring the course of disease and drug response.

The prognosis of these tumors is dismal and fatal in almost all cases, with an average overall survival of 6.7 months.¹⁵ The tumors are chemoresistant to a large group of drugs that are part of the treatment for germ cell tumor and epithelial malignancies. Further research on the response to histone deacetylase inhibitors, which restore acetylation, and bromodomain and extraterminal inhibitors which act by inhibiting bromodomain–acetyl histone binding, is underway.¹⁰

Conclusion

The present case scenario highlights the rarity and the diagnostic challenge these cases present. Correct diagnosis is imperative for therapeutic and prognostic implications.

Patient Consent

Retrospective analysis and the identity of the patient is not disclosed, hence consent not required.

Conflict of Interest

None declared.

References

- Moreno V, Saluja K, Pina-Oviedo S. NUT carcinoma: clinicopathologic features, molecular genetics and epigenetics. *Front Oncol* 2022;12:860830
- Matsuura H, Makimoto G, Oda N, et al. A prompt diagnosis and treatment of a case of nuclear protein of the testis carcinoma characterized by a bronchial lesion and high serum alpha-fetoprotein level following genomic testing. *Intern Med* 2024;63(19):2655–2660
- Fonseca D, Kodandapani S, Babu RV, Rao C, Rao S. Metastatic NUT carcinoma in a child. *Indian J Otolaryngol Head Neck Surg* 2023;75(03):2355–2358
- Chen J, Li M, Lu H. Nuclear protein in testis carcinoma of the lung. *Transl Oncol* 2023;30:101640
- Harada Y, Koyama T, Takeuchi K, Shoji K, Hoshi K, Oyama Y. NUT midline carcinoma mimicking a germ cell tumor: a case report. *BMC Cancer* 2016;16(01):895
- Agaimy A, Haller F, Renner A, Niedermeyer J, Hartmann A, French CA. Misleading germ cell phenotype in pulmonary NUT carcinoma harboring the ZNF532–NUTM1 fusion. *Am J Surg Pathol* 2022;46(02):281–288
- D'Ambrosio L, Palesandro E, Moretti M, et al. Alpha-fetoprotein elevation in NUT midline carcinoma: a case report. *BMC Cancer* 2017;17(01):266
- Murano C, Suzuki S, Nakamura S, Takeda H, Fukui T, Yoshioka T. Vimentin-positive and alpha-fetoprotein-elevated nuclear protein of the testis midline carcinoma: a case report and review of the literature. *Intern Med* 2021;60(22):3645–3649
- Oualla K, Messoudi K, Acharfi N, et al. Nuclear protein in testis midline carcinoma simulating germ cell tumor of the mediastinum. *Case Rep Clin Med* 2018;7:288–296
- Parikh SA, French CA, Costello BA, et al. NUT midline carcinoma: an aggressive intrathoracic neoplasm. *J Thorac Oncol* 2013;8(10):1335–1338
- Gasljevic G, Matter MS, Blatnik O, Unk M, Dirnhofer S. NUT carcinoma: a clinical, morphological and immunohistochemical mimicker—the role of RNA sequencing in the diagnostic procedure. *Int J Surg Pathol* 2022;30(03):273–277
- Zhu B, Laskin W, Chen Y, et al. NUT midline carcinoma: a neoplasm with diagnostic challenges in cytology. *Cytopathology* 2011;22(06):414–417
- Ma C, Jin Y, Wang Y, Xu H, Zhang J. Beyond liver cancer, more application scenarios for alpha-fetoprotein in clinical practice. *Front Oncol* 2023;13:1231420
- Raza A, Cao H, Conrad R, et al. Nuclear protein in testis midline carcinoma with unusual elevation of α -fetoprotein and synaptophysin positivity: a case report and review of the literature. *Expert Rev Anticancer Ther* 2015;15(10):1199–1213
- Lai JK, Panasci L, Patey NG, Wang H. Placental metastasis from maternal NUT carcinoma: diagnostic pitfalls and challenges. *BMJ Case Rep* 2024;17(04):e259538
- Ball A, Bromley A, Glaze S, French CA, Ghatage P, Köbel M. A rare case of NUT midline carcinoma. *Gynecol Oncol Case Rep* 2012;3:1–3