Medical and Research Publications
International Open Access

Case Report **Journal of MAR Oncology (Volume 4 Issue 5)**

Bizarre Treatment Response of BRAF Mutated Anaplastic Thyroid Carcinoma in an Adult Male. A Case Report with a Brief Review of the Literature.

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Received Date: October 06, 2022

Published Date: November 01, 2022

Abstract:

Anaplastic thyroid carcinoma is a rare undifferentiated malignancy of the thyroid gland, despite a lot of pharmacological advances in the field of Oncology; it is still considered one of the highly aggressive malignant tumors. 5-year survival is not more than 5% and most of the cases die within a year of the diagnosis. Here, we are presenting a case of 56 years old male who was diagnosed as Denova advanced Anaplastic thyroid carcinoma with lung Mets. Next-generation sequencing revealed BRAF V600E mutated lesion. Despite having excellent local control of the disease, metastatic lesions started rapidly growing and finally patient died within 3 months of the treatment. As per our knowledge, this is the first case documenting excellent control of the local disease but the rapid progression of the distant Mets in a thyroid malignancy.

Conclusion: *Our case presents scenario of heterogeneous discordancy to the treatment which is unusual in thyroid but common in cancers like breast and malignant melanoma. Further studies are needed to highlight this issue as it will have a strong impact on the treatment approach.*

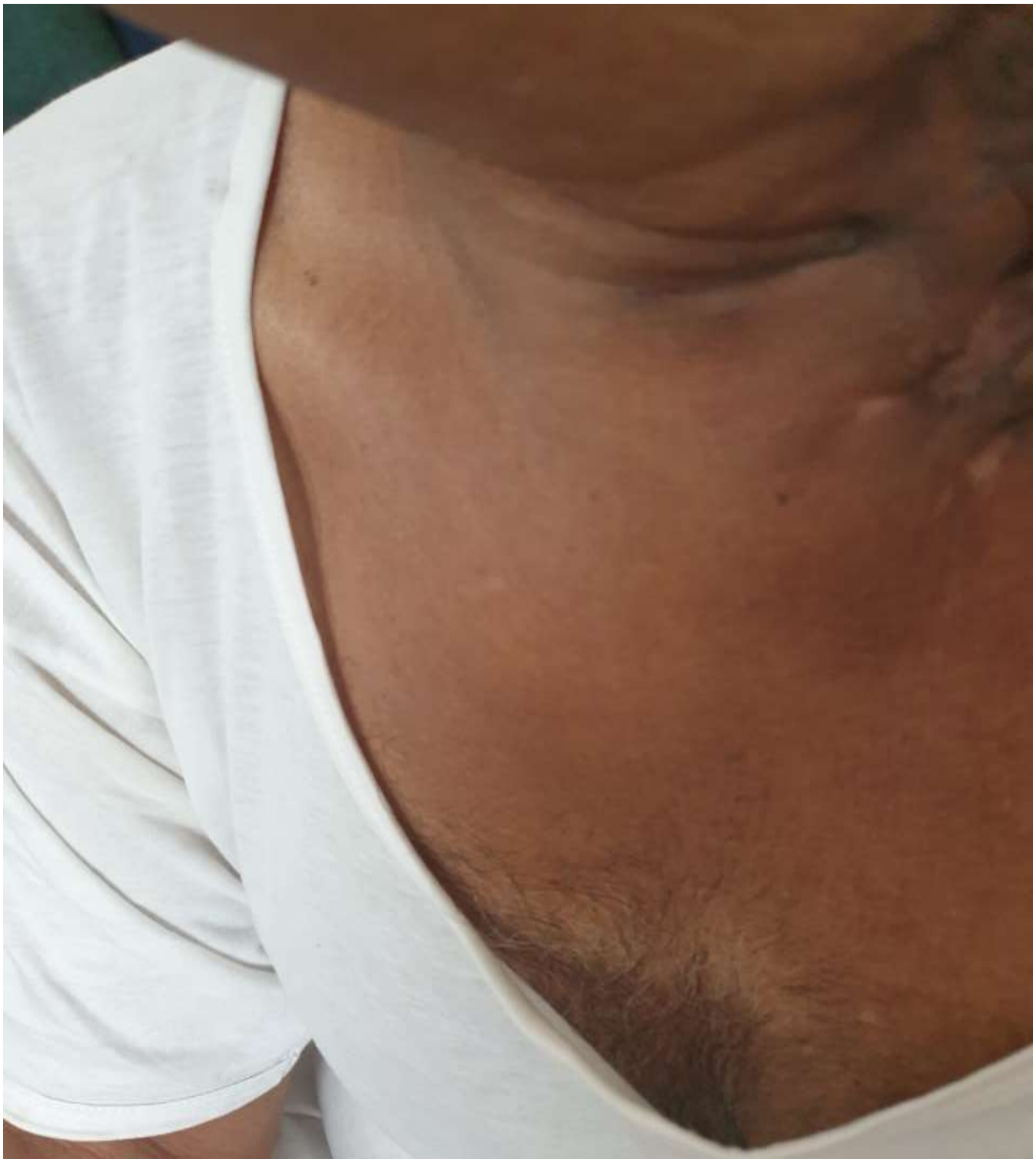
Keywords

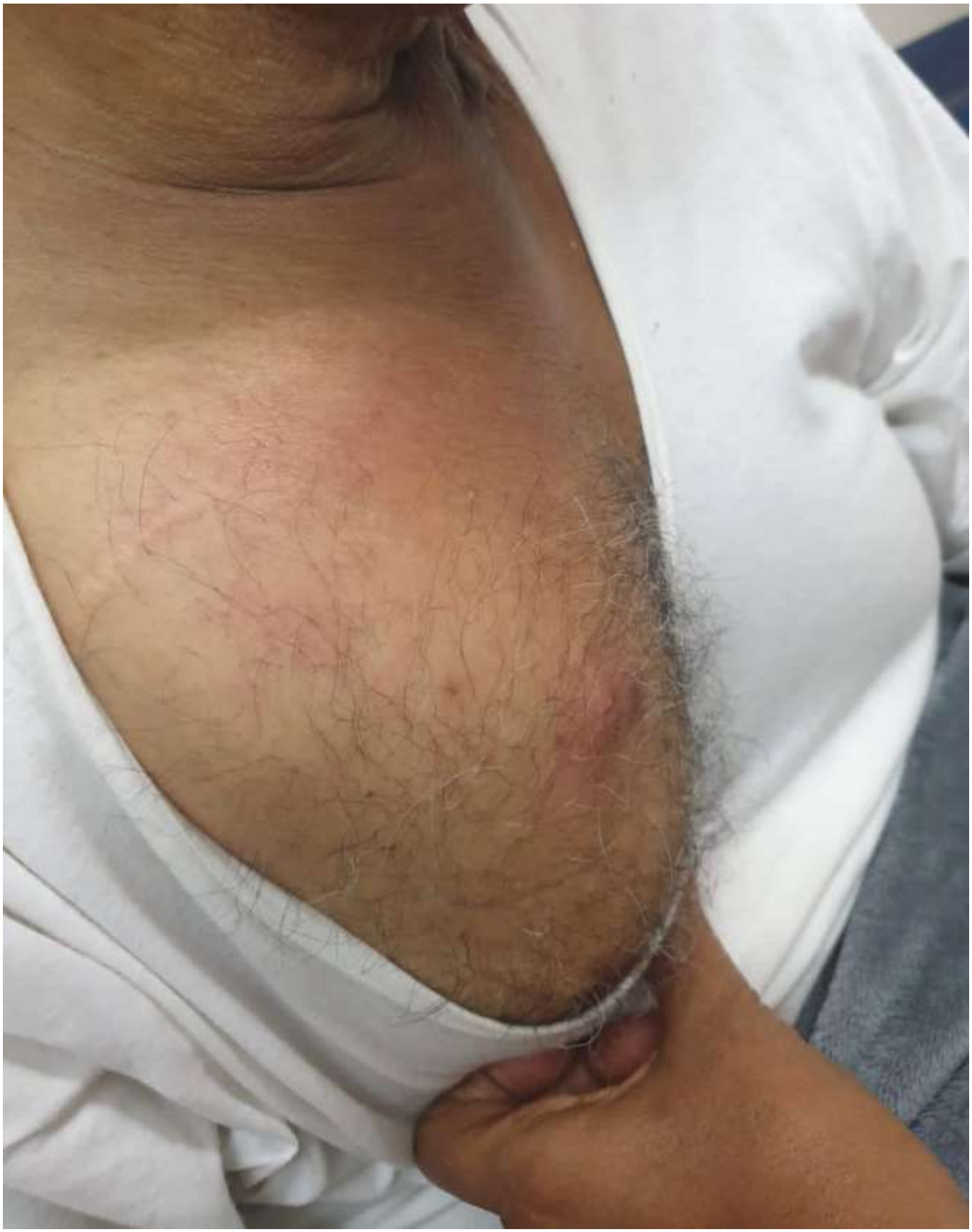
Anaplastic Thyroid carcinoma [ATC], Next generation sequencing [NGS], BRAF mutation.

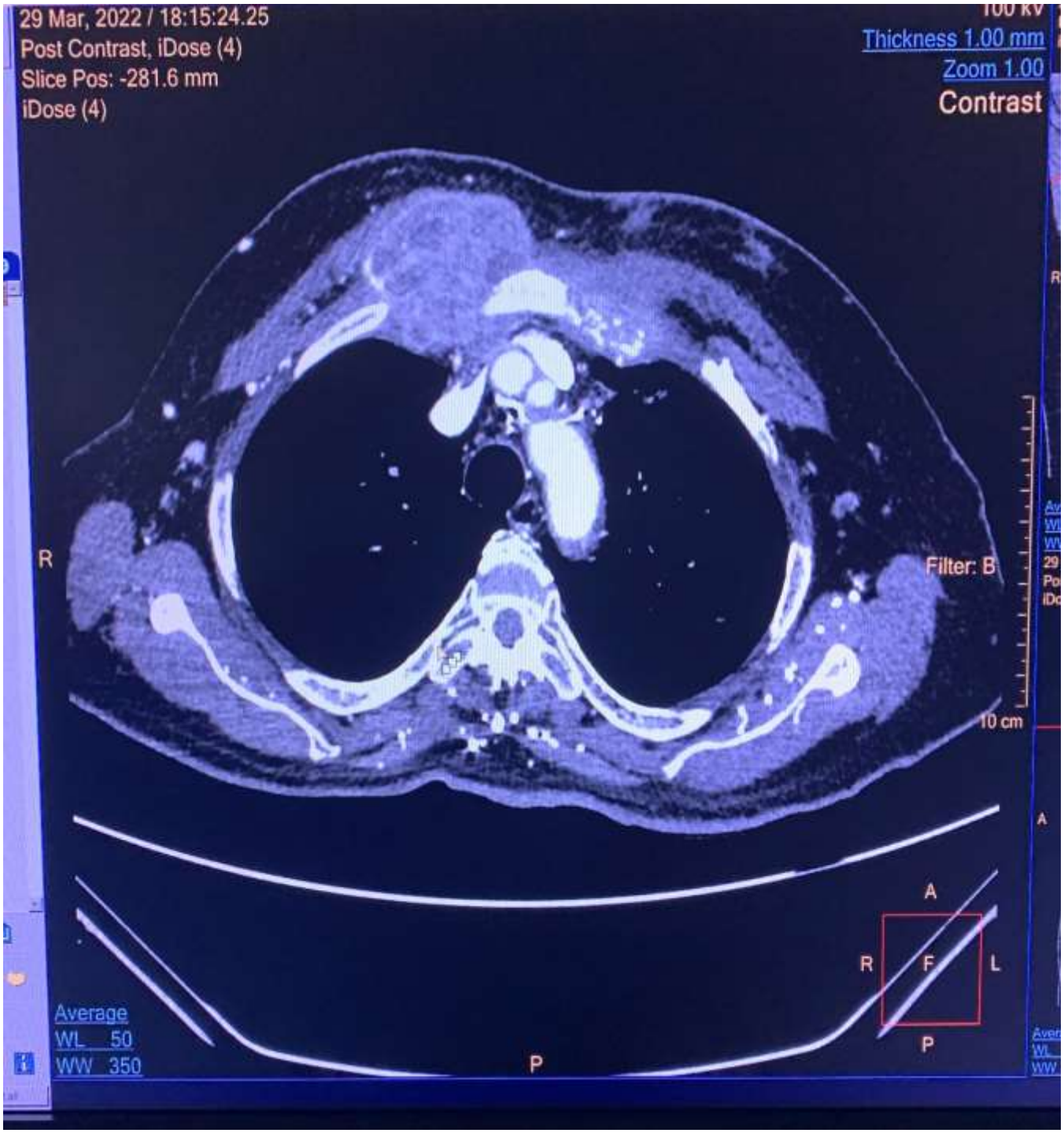
Case Presentation

56 years old gentleman known diabetic, non-smoker. He presented to our Oncology department a few months back with a worsening thyroid swelling surrounded by multiple skin nodules [Fig:1]. As per the clinical history and outside documents swelling had started 6 months back. The biopsy from skin nodules and thyroid was suggestive of poorly differentiated carcinoma of unknown origin. He was initiated on Taxol /carboplatin and after three cycles assessment revealed both clinical as well as radiological progression. The patient was seen in our Oncology OPD and further workup was initiated. A review of the biopsy was suggestive of anaplastic thyroid carcinoma. The sample was sent for next-generation sequencing and molecular analysis revealed BRAFp.V600E mutation.

The patient was started on Dabrafenib and Tramatenib and after 2 months only he had excellent improvement in his performance and a marked improvement in his thyroid swelling with the disappearance of tumor nodules. [Fig:2]. He was continued with the same treatment, however during the 3rd month of the treatment he started developing Right-sided chest wall swelling [Fig 3, Fig 4] [CT Thorax with contrast was done at the same time which revealed Right Paramidline anterior chest wall heterogeneously enhancing mass with calcified foci causing underlying rib destruction and soft tissue invasion]. Initially, it was thought we may be dealing with a case of pseudoprogression as is commonly seen during immunotherapy but this was soon realized far from truth as patient had rapid deterioration of his health and worsening of chest wall lesion [Fig:5] .Rebiopsy of the lesions was thought of but the condition of the patient didn't permit any interventional procedure. He also received palliative radiotherapy to the chest wall without any benefit and unfortunately the patient died within 3 months of starting anti- BRAF therapy.



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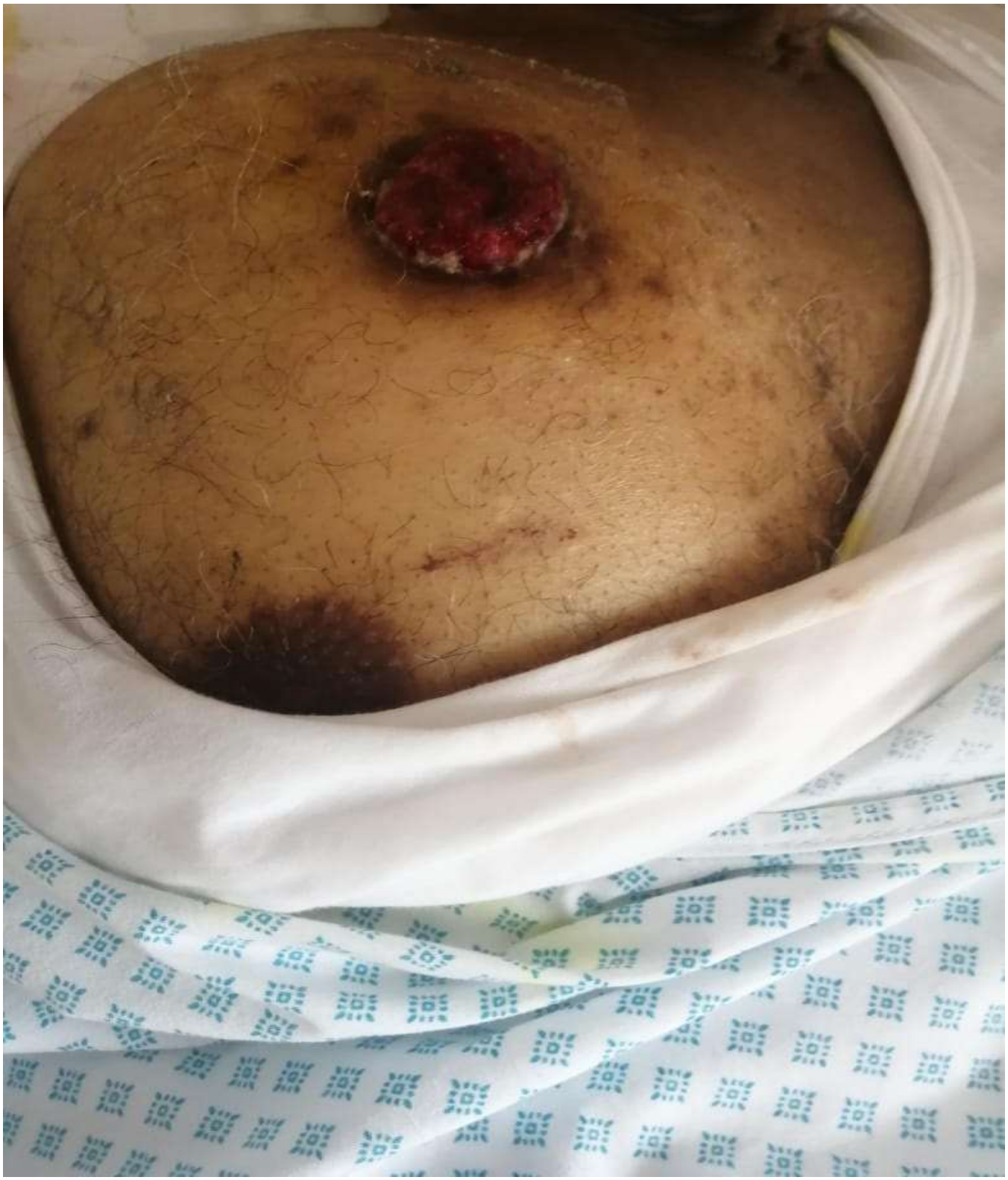

Review of the literature:

Anaplastic thyroid carcinoma is the name that still creates fear in the treating oncologist. Despite advances in the field of Medical Oncology, nothing works much for this cancer. Many cases arise as Denova but most of the cases can be traced back with origin from PTC as dedifferentiated cancer [1]. Except for the age and radiation exposure very little is known about the risk factors for this deadly disease. It tends to be common over the age of 60 years. Luckily the incidence of this cancer is decreasing because of early and proper management of differentiated cancers as well as proper intake of diet rich in Iodine [2, 3].

The rarity of this disease and its rapid progression have been an important hurdle in finding the treatment paradigm for this disease.[4] The treatment landscape for advanced ATC is changing and often involves next-generation sequencing and finding a target to achieve the response. Recently most of the international guidelines are recommending mutation testing to determine any driver mutation. [5,6]. Therapy is tailored to the individual patients and the presence of driver mutation in them. Given the BRAF V600E mutation rate of up to 50% in ATC, inhibition of MAPK cellular pathway has an important molecular target for Anaplastic thyroid carcinoma. A BRAF mutation analysis is mandatory, but a broader spectrum of tumor mutational status is preferred. . The phase II ROAR basket trial led to the approval of dabrafenib plus trametinib in BRAF V600E-mutant ATC. Investigator-assessed responses were observed in 56% of patients, with 50% of responders still in response at 12 months. Median OS was 15 months, with a 12-month rate of 52%.

The updated analysis after 4 years of intense follow up confirmed the benefit of Dabrafenib plus Trametinib in ATC. The study confirmed the substantial clinical benefit and manageable toxicity of dabrafenib plus trametinib in BRAF V600E-mutant ATC. The treatment improved long-term survival in these patients. Despite this, some patients have a very rapid progression as seen in our case also. We assume discordancy of BRAF mutation status as seen in melanoma has the same implication in thyroid cancer as in these tumors and it needs further study [7]. This may be one of the reasons for treatment failure in some cases. Even tumor heterogeneity may reflect this behavior as we have seen in other cancers like breast and lung. Further studies need to address this phenomenon. There have been cases where discontinuation of treatment has led to rapid progression [8] but in our case treatment was never discontinued.

Summary

The case highlights a new phenomenon even in the thyroid malignancy were in primary may respond but distant lesion will have a rapid progression. What is the reason is yet to be established? Is it discordancy, heterogenicity or hyperprogression more studies need to address this issue? The implication on its treatment in malignancy like ATC cannot be ignored.

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