CASE REPORT

SCLC, Paraneoplastic Dermatomyositis, Positive Transcription Intermediary Factor 1-γ, and Point Mutation in the Transcription Intermediary Factor 1-γ Coding Gene: A Case Report

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ABSTRACT

SCLC is frequently associated with paraneoplastic syndromes, including dermatomyositis. Patients with malignancy-associated dermatomyositis express a specific autoantibody pattern usually positive for anti–transcription intermediary factor 1-γ (TIF1-γ), suggesting anti–TIF1-γ plays a role in development of malignancy-associated dermatomyositis. We present a case of a patient with SCLC, paraneoplastic dermatomyositis, positive anti–TIF1-γ, and a point mutation in TIF1-γ coding gene, with prominent clinical response to chemoradiation. We suggest that this point mutation is pathogenic, providing evidence for the development of paraneoplastic dermatomyositis through immune cross-reactivity.

Keywords: Small cell lung cancer; Dermatomyositis; Anti-TIF1-γ; Case report

Introduction

SCLC is a highly aggressive cancer, frequently associated with paraneoplastic syndromes.[1] Dermatomyositis is an inflammatory disorder involving muscle weakness and typical skin rash and is often a manifestation of underlying malignancy, in particular SCLC.[2,3] Patients with malignancy-associated dermatomyositis (MAD) have worse clinical symptoms, are unresponsive to corticosteroid treatment, and have worse prognosis.[3] Patients with MAD express a distinct autoantibody pattern usually negative for dermatomyositis-specific autoantibodies yet positive for anti–transcription intermediary factor 1-γ (TIF1-γ), suggesting anti–TIF1-γ plays a role in MAD development.[4] Nevertheless, the underlying mechanism remains unclear. We present a case of a patient with SCLC, paraneoplastic dermatomyositis, positive anti–TIF1-γ, and a mutation in the TIF1-γ coding gene.

Case Presentation

A 68-year-old male heavy smoker was evaluated on June 2020 for an itchy rash on sun-exposed areas, which started 3 weeks before his referral, accompanied by

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proximal muscle weakness with inability to walk. Skin biopsy result revealed hyperkeratosis, vacuolar degeneration, and perifascicular muscle inflammation with monoclonal infiltration. He was treated with high-dose corticosteroids for 12 days (methylprednisolone 1 mg/kg twice a day for 2 d followed by prednisone 1 mg/kg once a day for 10 days) with little to no improvement.

Chest radiograph result revealed an oval opacification in the left lung, and result from a positron emission tomography-computed tomography-fluorodeoxyglucose revealed a left upper lobe heterogeneous lung mass 4.9 cm in diameter with standard uptake volume maximum of 13 Hounsfield unit (Fig. 1*A*). In addition, transbronchial biopsy result revealed SCLC features with a mitotic index of 60%. Consequently, the patient was admitted to the oncology ward.

On examination, the patient had scaly erythematous-confluent rash on his face, arms, and thighs together with hallmark shawl and V signs (Fig. 2*A*). There were proximal limb muscle weakness at two of five and laryngeal weakness with solid food dysphagia. Blood tests were prominent for creatinine kinase (CK) at 4842 U/liter (reference range; 22–198 U/liter), and a complete rheumatologic panel was positive for anti–TIF1-γ 64 U and negative for other dermatomyositis-specific autoantibodies.

Because of the clinical features, elevated CK, positive anti–TIF1-γ, and findings of muscle and lung pathologies, the patient was diagnosed as having limited SCLC with paraneoplastic dermatomyositis. The patient was treated with cisplatin (75 mg/m^2 once a day) and etoposide (100 mg/m^2 once a day for three days). One week after admission, the patient began to have improvement

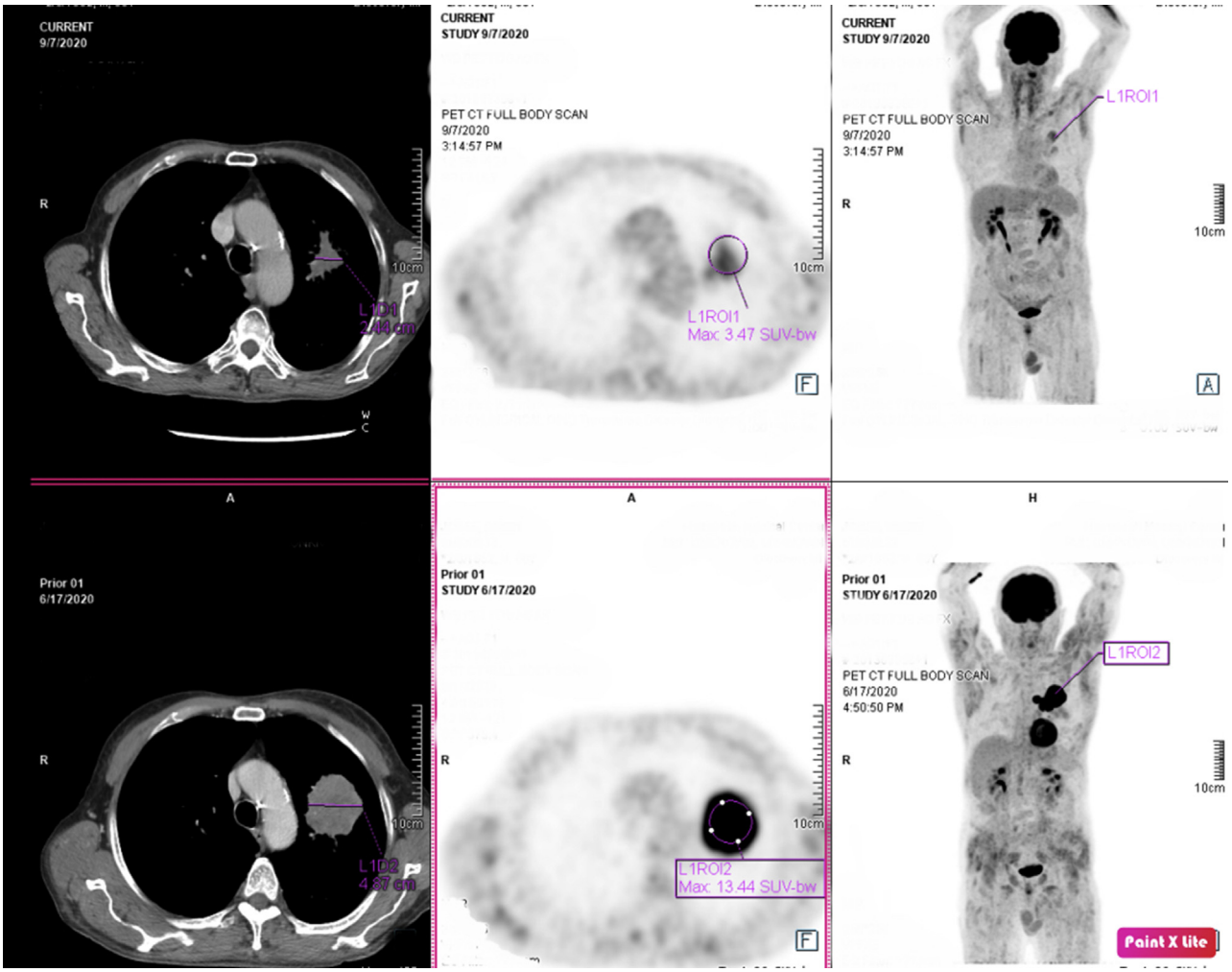

Figure 1. PET-CT-FDG results of the patient. (*A*) During initial diagnosis on June 2020 revealing tumor size of 4.87 cm and uptake of 13.4 HU. (*B*) Follow-up PET-CT on September 2020 after chemoradiation treatment revealing reduction in tumor size to 2.4 cm and uptake to 3.4 HU. CT, computed tomography; FDG, fluorodeoxyglucose; HU, Hounsfield unit; PET, positron emission tomography; SUV, standard uptake volume.

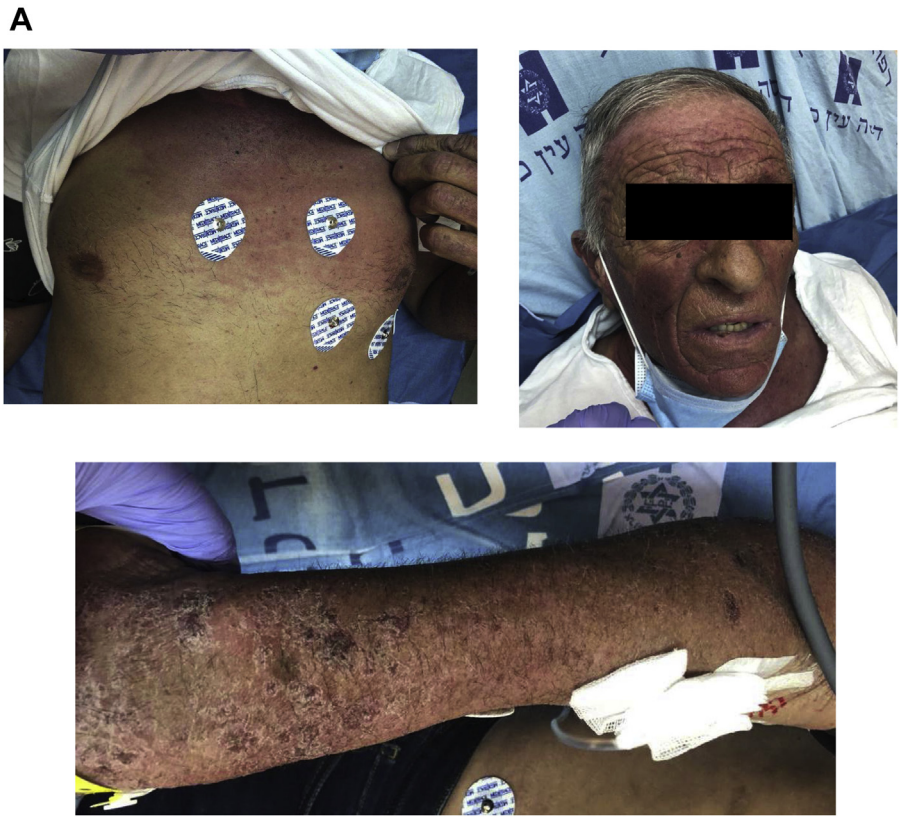

Figure 2. (*A*) Pictures taken during initial presentation on June 2020 revealing scaly erythematous-confluent rash, shawl, and V signs. (*B*) Pictures taken during follow-up on September 2020 after completion of chemoradiation revealing improvement in rash on hands, face, and chest.

in his symptoms, including improvement of the rash, renewed ability to walk with a walker, and sallow solid food. CK level was down to 1300 U/liter.

In July to September 2020, the patient completed three more cycles of cisplatin-etoposide with concurrent radiotherapy, for a total dose of 66 Gy. On follow-up examination done on September 2020, there was complete resolution of the rash (Fig. 2*B*), improvement of proximal strength, and the patient was now able to walk unaided. CK levels were normalized, and anti–TIF1-γ levels were reduced from 64 U measured during the initial diagnosis 3 months earlier to 19 U measured on follow-up. Result from repeat positron emission tomography-computed tomography-fluorodeoxyglucose revealed reduction of tumor size and uptake to 2.4 cm with standard uptake volume of 3.4 Hounsfield unit (Fig. 1*B*).

Whole-gene next-generation hybrid-capture DNA and RNA sequencing (next-generation sequencing [NGS]) analysis was performed on the tumor sample obtained from transbronchial biopsy. There were *RB1* and *P53* loss-of-function mutations and *MYC* copy number gain with a corresponding MYC and TOP2A overexpression. Furthermore, there was a missense point mutation c.2519T>C in the TIF1-γ coding gene, *TRIM33* with matching RNA mutation with median gene coverage of 462 (25–75 percentile in 124–575 coverage, accordingly).

Discussion

We presented a case of a patient with newly diagnosed limited SCLC with a prodrome of paraneoplastic dermatomyositis, positive anti–TIF1-γ, and a mutation in the TIF1-γ coding gene. Impressive response to chemoradiation was evident in clinical features of dermatomyositis, imaging of primary tumor, and reduction of anti–TIF1-γ.

TIF1-γ is a regulator of cellular proliferation and is considered a tumor suppressor, through its regulation of the TGF-β and Smad pathway, by its ability to ubiquitinate or compete with Smad3 or 4. Inactivation, mutation, or down-regulation of TIF1-γ results in tumorigenesis and metastasis development, as evident in several malignancies.[5]

The mutation p.I840T found in this case is located near the plant homeodomain of TIF1-γ (Fig. 3). Using SWISS-MODEL, we predicted that this mutation would modify protein structure and binding. In vitro studies have revealed that ubiquitination of Smad4 by TIF1-γ is

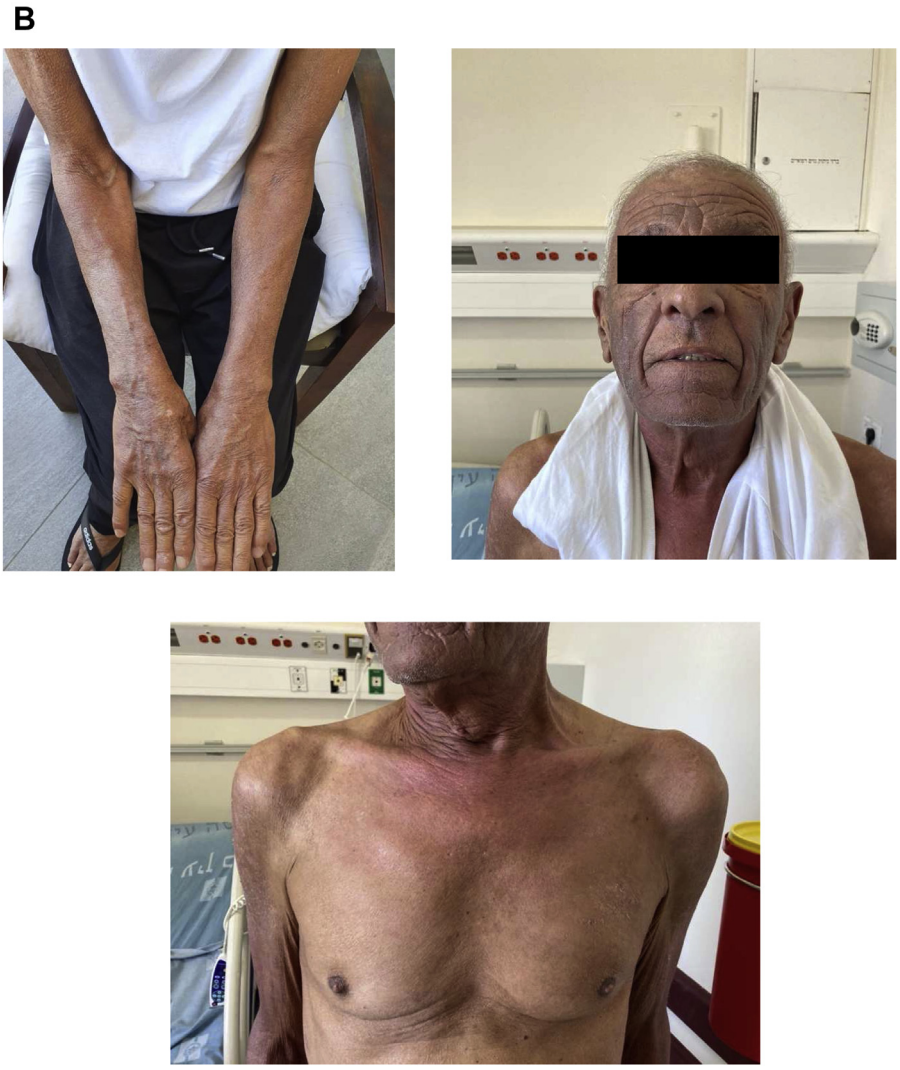

Figure 2. Continued.

dependent on integral binding of plant homeodomain to Smad4. In addition, loss of TIF1-γ attenuates down-regulation of *MYC*,[5] which was found to be overexpressed in our case.

Pan-cancer search of cBioPortal.org and Catalogue Of Somatic Mutations In Cancer found that although *TRIM 33* mutations occur in less than 1% of cancers, p.I840T appears with the most frequency, including in 84 cases of non-SCLC and 37 cases of endometrial cancer harboring improved prognosis. These results suggest that the mutation found in our case is likely pathogenic. A point mutation c.3299T>C in *TRIM33* has been previously described in one other patient diagnosed with having MAD with positive anti–TIF1-γ yet, with unknown clinical context or recurrence of this mutation in other malignancies.

Anti–TIF1-γ is highly specific to MAD and reacts with TIF1-γ antigens found mostly in skin and muscle tissues. Hence, it is suggested that the immune response to altered TIF1-γ in the tumor cross-reacts with native TIF1-γ antigens in muscle and skin tissues, causing MAD.[4] The likely pathogenic mutation found in our case and the anti–TIF1-γ reduction in response to treatment provide important evidence for this hypothesis. Furthermore, cross-reactivity is considered to be the mechanism causing neurologic paraneoplastic syndromes.[1] To the best of our knowledge, none of the exciting NGS panels contain *TRIM33*. We suggest that this gene be added to NGS panels owing to its importance as a tumor suppressor and a marker for paraneoplastic syndromes.

Conclusion

The mutation c.2519T>C in *TRIM33* is likely pathogenic and provides evidence of the development of MAD through

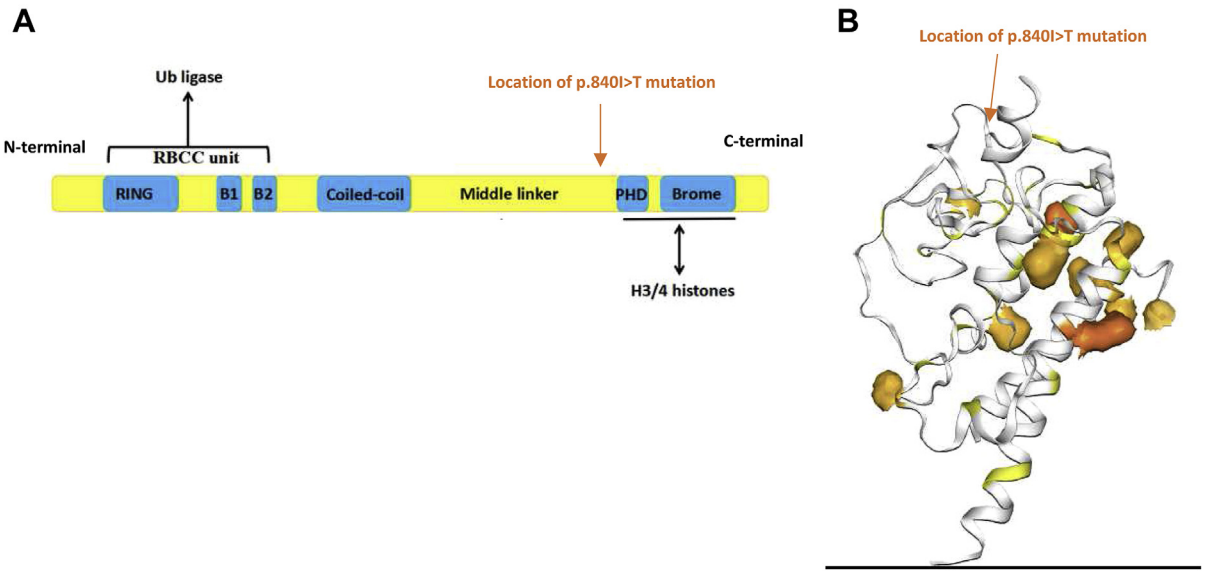

Figure 3. (*A*) Schematic representation of TIF1-γ protein containing a ubiquitin ligase with a ring-box-coiled coil region on the n-terminal and a PHD and bromodomain with high H3 chromatin affinity on the c-terminal. Location of point mutation found in our case p.840I>T noted in orange. (*B*) 3D representation of TIF1-γ. PHD/bromodomain-histone complexes represented in dark orange. Taken from COSMIC. Location of point mutation found in our case p.840I>T noted in orange. 3D, three dimensional; COSMIC, Catalogue Of Somatic Mutations In Cancer; PHD, plant homeodomain; TIF1-γ, transcription intermediary factor 1-γ.

immune cross-reactivity. Future analysis of *TRIM33* in NGS panels might provide further proof for this finding.

CRediT Authorship Contribution Statement

Johnathan Arnon: Conceptualization, Investigation, Writing—original draft.

Anna Elia: Resources.

Yuval Nevo: Investigation, Formal analysis.

Alexander Lossos: Resources, Investigation, Writing—review and editing.

Hovav Nechushtan: Conceptualization, Supervision, Writing—review and editing.

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