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Artificial intelligence (AI) molecular analysis tool assists in rapid treatment decision in lung cancer: a case report

Barliz Waissengrin,[1,2] Alexandra Garasimov,[1] Or Bainhoren ,[1,2] Ofer Merimsky,[1,2] Sivan Shamai,[1,2] Ariel Erental,[2,3] Ido Wolf,[1,2] Dov Hershkovitz[2,3]

[1]Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]School of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Pathology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Correspondence to
Dr Barliz Waissengrin, Oncology Division, Tel Aviv Sourasky Medical Center, Tel Aviv 6423906, Israel; barlizw@tlvmc.gov.il

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ABSTRACT

Leptomeningeal involvement among non-small cell lung cancer (NSCLC) patients is an aggressive form of disease that requires quick and efficient treatment. In this case report, we describe a woman in her 40s with a presenting symptom of headache that ultimately was diagnosed as leptomeningeal spread from NSCLC adenocarcinoma. We identified EGFR mutation in less than 48 hours from the biopsy using imagene-artificial intelligence's real-time algorithmic solution on the pathological diagnostic slide.

INTRODUCTION

Leptomeningeal spread is one of the most devastating complications of non-small cell lung cancer (NSCLC) with incidence rates reaching 3.8% in molecularly unselected NSCLC patients and up to 9% in *EGFR*-mutant cases.[1 2] Treatment possibilities include whole axis cranial irradiation, systemic chemotherapy and intrathecal chemotherapy.[3] These treatments have the potential for high rates of side effects, including cognitive deterioration, memory disturbance and severe myelosuppression, along with low response rates.[4 5] For the unique group of patients whose tumours harbour *EGFR* mutation, the treatment may include the targetable tyrosine kinase inhibitor (TKI) drugs as first-line treatment.

Treatment with the third-generation TKI osimertinib was proven as an efficient treatment of leptomeningeal spread among *EGFR* mutated NSCLC patients. Data from the phase I prospective BLOOM Study (with osimertinib dose of 160 mg) and from the retrospective analysis of the AURA studies (with osimertinib dose of 80 mg) for the cohort of patients with leptomeningeal spread showed response rates of up to 55% with clinical benefit for neurological symptoms.[6 7] As a result of the high cranial response rate, it is possible to consider the omission of radiotherapy and, by that, avoidance of the substantial side effects.

CLINICAL SUMMARY

In July 2022, a healthy woman in her early 40s with no history of smoking was admitted to the emergency room due to worsening headaches over the last month. Her neurological examination and blood work, including electrolytes, complete blood count and CRP, were all normal. Lumbar punctures showed minimally high pressure (230 mmH2O), with a few atypical cells. Gynaecological and breast ultrasonography were normal. Brain MRI showed leptomeningeal enhancement as an indication of leptomeningeal spread (figure 1A). A total body CT scan showed a mass in the apex of the left lung of approximately 2.6 cm diameter. No other suspicious lesions were identified. A biopsy from the mass in the lung gave a diagnosis of adenocarcinoma (figure 1B). The multidisciplinary team discussed the potential approaches. The extensive brain involvement required rapid treatment, with whole neuroaxis irradiation considered as an option. However, the patient's young age and no smoking history puts her at a high chance of harbouring a targetable driver mutation raising the possibility of treatment with TKIs. To assess whether the patient's tumour indeed carries a targetable alteration, the greater part of the biopsied tissue was sent for comprehensive genomic testing. However, since the patient needed immediate intervention, she could not afford waiting the 7–14 days for the comprehensive genomic profiling (CGP) results.

On February 2023, another healthy woman in her early 40s with no history of smoking was admitted to the emergency room due to headache, visual disturbance and nausea. Her neurological

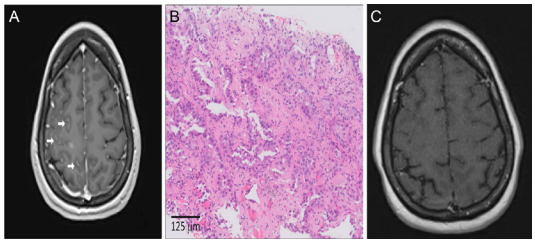

Figure 1 MRI and pathology slide image of a female patient in her early 40s diagnosed with lung metastatic cancer. (A) Brain MRI. T1 brain MRI after gadolinium injection showing nodular enhancement of the sulci of the right hemisphere. Arrows indicate masses. (B) Representative section of the H&E-stained slide of the biopsied specimen obtained from the mass in the left lung showing atypical glandular structures compatible with adenocarcinoma. (C) Brain MRI after 2 months of TKI treatment. T1 brain MRI after gadolinium injection without nodular enhancement of the sulci of the right hemisphere. Arrows indicate the previous sites of the spread. TKI, tyrosine kinase inhibitor.

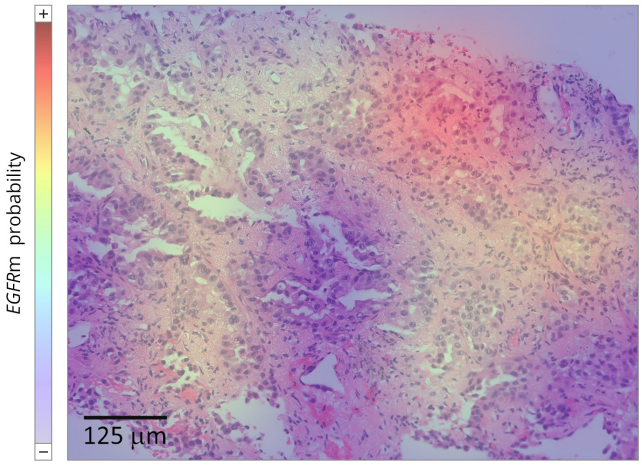

Figure 2 AI inference heat map. Representative patch of heat map image over the H&E showing areas predicted to be *EGFR*-positive (*EGFR* mutation (*EGFR*m) probability). AI, artificial intelligence.

examination revelled lateral rectus nerve palsy and papilledema. Lumbar punctures showed high pressure (345 mmH2O), with epithelial malignant cells. Brain MRI showed leptomeningeal enhancement as an indication of leptomeningeal spread (figure 1A). A total body CT scan showed a hilar mass in her LUL. A biopsy from the mass in the lung gave a diagnosis of adenocarcinoma. again, a rapid diagnosis and molecular testing was needed in order to treat appropriately.

PATHOLOGICAL FINDINGS

In both cases, to allow prompt decision without compromising the small amount of remaining tissue, we leveraged Imagene-artificial intelligences (AI's) real-time algorithmic solution on the pathological diagnostic slide to guide specific gene testing decisions. For this analysis, deep learning algorithms were trained to infer genomic alteration status within regions of interest in the scanned image of the H&E-stained slide. The algorithmic inference identified positivity for *EGFR* mutation.figure 2 A subsequent rapid PCR test for *EGFR* mutations (Idylla *EGFR* assay, Biocartis, Mechelen, Belgium) was indeed positive for the common *EGFR* L858R exon 21 mutation. Consequently, the patients started treatment with a TKI within 2–4 days from the biopsy, averting the need for CNS irradiation. Both patients' MRI scans after 2 months of TKI showed significant improvement with disappearance of the enhancement (figure 1C).

DISCUSSION

Pathological CGP is currently the assay of choice for advanced NSCLC patients, covering multiple targetable somatic alterations. However, CGP is time-consuming, with the time for diagnosis reaching up to 4 weeks. A more focused assay may provide more rapid results, even on the same day; however, many times, the amount of tissue in the biopsy is limited, thus not allowing analysis for all the targetable alterations.

Here, we describe the use of a novel approach using AI analysis on the routine diagnostic H&E-stained slide image to directly detect actionable genomic alterations. To the best of our knowledge, this is the first report demonstrating a clinical use of an AI application for directing the choice of molecular diagnostic assay. Applying an AI solution in cases, such as the one described here, where time is of the essence and the biopsied specimen is limiting, can be extremely advantageous as it is both immediate and tissue independent. Integrating such solutions in clinical practice can assist in testing prioritisation (in this case, performing a fast *EGFR* RT-PCR test) and expedite the identification of molecular alterations that guide critical treatment decisions. As technology progresses and digitalisation is becoming widely adopted, AI applications are gradually being introduced into the diagnosis workflow.[8] The adoption of such new tools in the clinical workflow toolkit has the potential to dramatically improve the routine pipeline and enhance the abilities of physicians to provide optimal patient care (figure 3).

A patient in her early 40s was admitted to the hospital with severe headaches. On medical workup, brain MRI and total body CT scan revealed suspected metastatic lung cancer. Trans thoracic biopsy from the lung mass identified the tumour as NSCLC adenocarcinoma. Treatment options included whole neuroaxis radiation therapy or systemic targeted therapy. However, the latter requires next-generation sequencing (NGS)

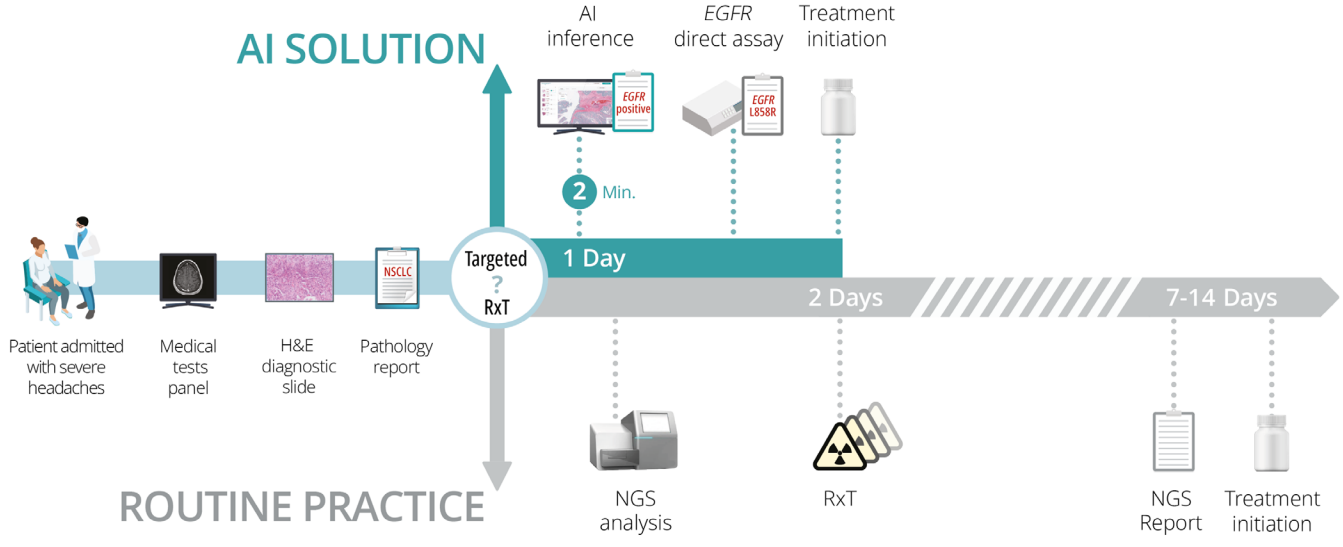

Figure 3 Schematic representation of the case. AI, artificial intelligence; RxT, artificial intelligence; NSG, next-generation sequencing.

testing that takes a minimum of 7 days. Due to the patient's critical condition, immediate intervention was required. Thus, a 2 min AI molecular inference solution (by Imagene AI) was used. The AI analysis performed on the diagnostic scanned H&E image reported a positive *EGFR* mutation, which supported the decision to test the remaining limited specimen with an Idylla direct *EGFR* assay. Indeed, an L858R mutation was identified. Due to the prompt analysis, the patient was administered osimertinib targeted therapy 2 days after the biopsy. The incorporation of the AI solution not only enabled targeted treatment 1 week earlier than in the routine practice but also resulted in avoiding altogether whole neuroaxis radiotherapy.

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ORCID iD

Or Bainhoren http://orcid.org/0000-0001-9910-5547

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