OPEN ACCESS

Symptomatic pseudoprogression in metastatic colorectal cancer

Kasen Hutchings,[1] Ajlan Al Zaki,[2] Nishin Bhadkamkar,[2,3] Jason Willis [3]

[1]Cancer Systems Imaging, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2]General Oncology, The University of Texas MD Anderson Cancer Center Division of Cancer Medicine, Houston, Texas, USA
[3]Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center Division of Cancer Medicine, Houston, Texas, USA

Correspondence to
Dr Jason Willis;
jason.willis@mdanderson.org

Accepted 1 May 2024

To cite: Hutchings K, Al Zaki A, Bhadkamkar N, *et al*. *BMJ Case Rep* 2024;**17**:e258816. doi:10.1136/bcr-2023-258816

SUMMARY

A man in his 70s with metastatic colorectal cancer presented with worsening clinical symptoms and imaging studies concerning for disease progression. He had received two cycles of pembrolizumab, but due to his symptomatic presentation and significant decline in performance status, there was concern for worsening disease. Transitioning to hospice was briefly considered, given his clinical decline and the notable increase in tumour size. Despite the presence of clinical symptoms and radiographic findings, pseudoprogression—defined as an increase in the size(s) of and/or visual appearance of new lesion(s), followed by a response—was also considered as part of the diagnostic possibilities. Consequently, the decision was made to proceed with a third cycle of pembrolizumab. During his subsequent outpatient follow-up, the patient showed significant symptomatic improvement and reported a decrease in his palpable right flank mass. With further immunotherapy, the patient continued to demonstrate symptomatic and radiological improvement.

BACKGROUND

Colorectal cancer (CRC) is the third leading cause of cancer-related death and the third most common cancer diagnosed in the USA.[1] While the majority of CRC diagnoses are considered to be sporadic, an estimated 6%–10% are associated with genetic predisposition due to pathogenic germline alterations in known hereditary CRC genes.[2]

Lynch syndrome is the most common hereditary CRC syndrome and is caused by pathogenic germline mutations in mismatch repair (MMR) pathway genes MLH1, MSH2, MSH6 or PMS2.[3–6] Somatic inactivation of the second MMR allele leads to the inability to repair errors in DNA replication, resulting in exceptionally high levels of missense mutations, frameshift mutations and microsatellite instability. This high mutation burden is also associated with the expression of tumour neoantigens, which lead to host immune cell recruitment and activation.[7] MMR deficiency may also occur sporadically through somatic bi-allelic inactivation of the MMR genes.

MMR-deficient CRC (both hereditary or sporadic forms) is a clinically and molecularly distinct subtype of the disease. Within the tumour microenvironment, chronic immune signalling can result in T cell exhaustion and progression of tumour growth.[8] Revitalisation of exhausted T cells via immune checkpoint inhibitor (ICI) therapy can restore immune response and has proven to be effective in the treatment of MMR-deficient cancers, including colon cancer.[9] ICIs that target cytotoxic T-lymphocyte associated antigen (CTLA-4), programmed death-1 and programmed death-ligand 1 (PD-L1) are among the most beneficial treatment options and have resulted in significant breakthroughs in cancer immunotherapy.[10–14]

Tumour response patterns following ICI therapy differ significantly from other cancer therapies. A common challenge in using these response patterns to assess ICI efficacy is pseudoprogression, which is conventionally defined in the literature as an initial increase in the sizes of existing lesions or visualisation of new lesions, followed by regression. This phenomenon is likely caused by infiltration of the tumour by immune cells and the subsequent release of cytokines, which can cause oedema and observable tumour growth.[15] Imaging modalities, including MRI, CT, positron emission tomography (PET) and ultrasound (US), are all used in diagnosing pseudoprogression; however, because pseudoprogression is typically diagnosed retrospectively, there is a significant period in which the patient remains at risk of misdiagnosis. In addition to imaging data, a diagnosis of pseudoprogression can be strengthened through histopathological biopsies of pseudoprogressive tumours, which have been shown to contain dense CD8, TIA1 and granzyme B lymphocyte infiltrates.[16–18] Another report of pseudoprogression histological analysis found infiltrated lymphocytes, which were positive for CD3, CD4 and CD8 in place of expected tumour cells.[19] Though they have been shown to yield immune cells in patients with pseudoprogression, biopsies are not typically part of routine clinical practice due to their invasive nature and limited efficacy. Diagnosis of pseudoprogression relies primarily on retrospective imaging and clinical judgement.

Initial reports indicated that the incidence of pseudoprogression was less than 10%[20–22]; however, a recent study[23] has shown that the rate of pseudoprogression may be as high as 20%. This high rate of pseudoprogression has led to the development of new immune-related response-evaluation criteria: iRECIST,[24] irRECIST[25] and irRC.[22] These criteria improve on the conventional criteria by permitting ICI therapy beyond progression, thus allowing for a more accurate assessment of ICI efficacy.[20] For example, using the iRECIST criteria, a target lesion growth equal to or greater than 20% would be classified as immunotherapy-related unconfirmed progressive disease (iUPD) and would necessitate a shorter interval (4–8 weeks) follow-up for reevaluation and possible diagnosis of pseudoprogression. In contrast to RECIST, iRECIST recommends continuation of immunotherapy following iUPD diagnosis. If progressive disease is not confirmed by continued growth of the lesion, the iUPD status remains, and follow-up should be performed at 8-week intervals until

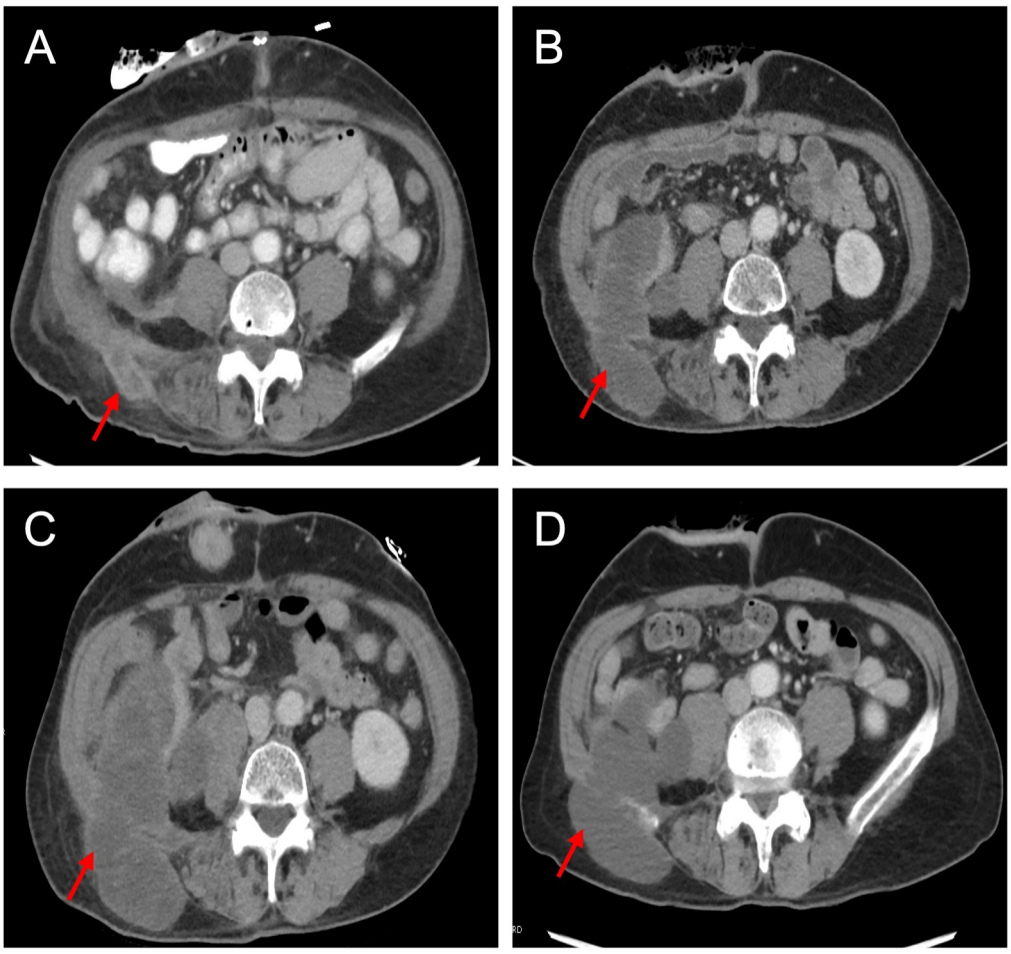

Figure 1 Axial CT sections showing right lower quadrant mass. (A) Initial residual lesion following total abdominal colectomy, (B) interval progression of right lower quadrant mass following four cycles of 5-fluorouracil and oxaliplatin, (C) interval growth showing multiloculate complex cystic mass following two cycles of pembrolizumab, (D) interval decrease in size of multiloculated complex cystic mass after six cycles of pembrolizumab.

progression, pseudoprogression or remission is confirmed. If there is tumour shrinkage at follow-up that meets iRECIST criteria for complete remission, partial remission or stable disease, the tumour loses its iUPD status until further growth is observed.[24 26]

Typically, pseudoprogression is associated with an improved general condition and decreased symptoms, whereas true progression is associated with persistent symptoms and patient deterioration.[27] Using iRECIST criteria, continued immunotherapy treatment beyond progression is only considered in special cases in which the patient is stable and improving symptomatically.[24] In this report, we outline the case of a patient with atypical, symptomatic pseudoprogression following ICI therapy for metastatic CRC, followed by significant symptom improvement and tumour regression with continued ICI therapy.

CASE PRESENTATION

We report on a male patient in his 70s who is being followed closely for management of adenocarcinoma of the cecum. He presented for an initial oncology visit after undergoing a total abdominal colectomy with end ileostomy at an outside hospital. Postoperative imaging demonstrated a 4.2×2.1 cm residual lesion in the right posterior flank subcutaneous aspect just superior to the iliac crest (figure 1A). He underwent interventional radiology-guided biopsy of a left posterior palpable flank mass confirming moderately differentiated adenocarcinoma with mucinous features. Due to unavailability of tissue samples, immunohistochemistry for MMR was not performed. The decision was made to proceed with systemic therapy while awaiting the results of next generation sequencing (NGS). Initially, he received four cycles of 5-fluorouracil and oxaliplatin. Unfortunately, restaging scans showed a significant interval increase in size of a multiloculated cystic mass in the right lower quadrant involving a segment of the small bowel and the right iliacus muscle, which protruded through the posterior abdominal fascia into the subcutaneous tissue, measuring approximately 5.2×10.4×9.9 cm (figure 1B). A second, likely separate, lesion measuring 2.8×2.1 cm abutting the right psoas was also found. Mutational testing on his tumour tissue using NGS revealed a PMS2 mutation (splice region variant, c.989–2A>G), KRAS mutation and high tumour mutational burden (46.8 mutations/MB, 99th percentile) with a PD-L1 tumour proportion score of 95%. Germline mutational testing confirmed an alteration in PMS2, consistent with a diagnosis of Lynch syndrome.

Pembrolizumab therapy was started; however, after the second cycle, the patient was admitted for fevers, worsening abdominal pain, melena from the ostomy and right lower extremity pain resulting in inability to ambulate. A CT scan showed interval growth of the multiloculated complex cystic mass, now measuring a maximum of 18 cm, involving a segment of the lower quadrant small bowel, and extending into the right psoas, iliacus, iliopsoas and posterolateral abdominal wall muscles (figure 1C.). Questionable small cystic

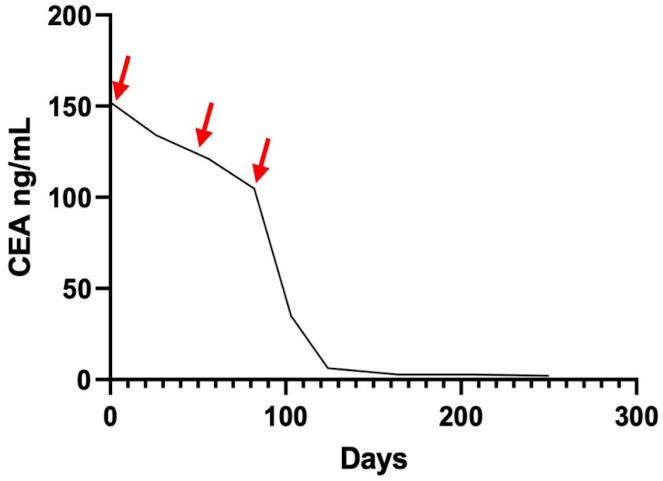

Figure 2 Graph of carcinoembryonic antigen (CEA) over duration of treatment. The first arrow (left) indicates CEA level after completion of surgery and prior to initiation of 5-fluorouracil and oxaliplatin (FOLFOX), the second arrow (middle) indicates CEA level after completion of four cycles of FOLFOX with radiographic evidence of progression and the third arrow (right) indicates CEA level after two cycles of pembrolizumab and admission with radiographic findings concerning for progression. Figure created by AAZ.

implants were seen along the serosal surface of the small bowel in the right abdomen anterior to the right kidney.

This apparent tumour progression led us to a crossroads with three clinical options: (1) continue pembrolizumab therapy despite apparent progression, (2) switch to an alternative form of therapy, (3) refer the patient to hospice and provide palliative care for symptom management. Despite the appearance of symptomatic and radiological progression, we questioned whether this was a case of pseudoprogression. After the rapid tumour progression following only two cycles of pembrolizumab, it was unclear whether sufficient time had elapsed to gauge the efficacy of immunotherapy. Therefore, outpatient follow-up was recommended to determine whether or not he would benefit from an additional cycle of pembrolizumab. During his outpatient follow-up, the patient had significant clinical improvement in his symptoms and reported a decrease in his palpable right flank mass (figure 1). In addition, his carcinoembryonic antigen level had significantly decreased, further confirming response to ICI (figure 2). Given these findings, we opted to continue with pembrolizumab.

OUTCOME AND FOLLOW-UP

He continues to benefit from ongoing treatment with his immunotherapy regimen with return to his baseline level of activity and independent of all of his activities of daily living. On last follow-up, he remains asymptomatic without any pain or discomfort. His most recent CT scan of the abdomen and pelvis (figure 3), after completion of 16 cycles of systemic therapy with pembrolizumab, continues to demonstrate an unchanged appearance of the complex irregular mass in the right paracolic gutter connecting with the right psoas muscle (measuring 3.2×3.0 cm), small bowel and iliacus (measuring 5.3×3.2 cm), and iliopsoas muscle (3×2.2 cm), extending into the subcutaneous fat of the right flank through the posterior medial abdominal wall (measuring 6.8×3.2 cm). In a subgroup analysis of KEYNOTE 177, which evaluated pembrolizumab in patients with MSI-high advanced CRC, individuals with KRAS/NRAS mutations did worse compared with wild-type.[28] Therefore, we opted to continue systemic therapy with pembrolizumab every 6 weeks with routine follow-up and 3 to 6-month imaging intervals. While there is a correlation between KRAS/NRAS mutations and resistance to pembrolizumab, the dynamics might differ with a broader RAS mutation spectrum and yield positive outcomes for this patient.

DISCUSSION

Radiographic findings concerning for disease progression or treatment failure can sometimes alter the course of cancer-specific therapy, potentially resulting in early therapy switching and worse patient outcomes. While the cancer initially appeared to be progressing, the patient began to benefit from ICI therapy

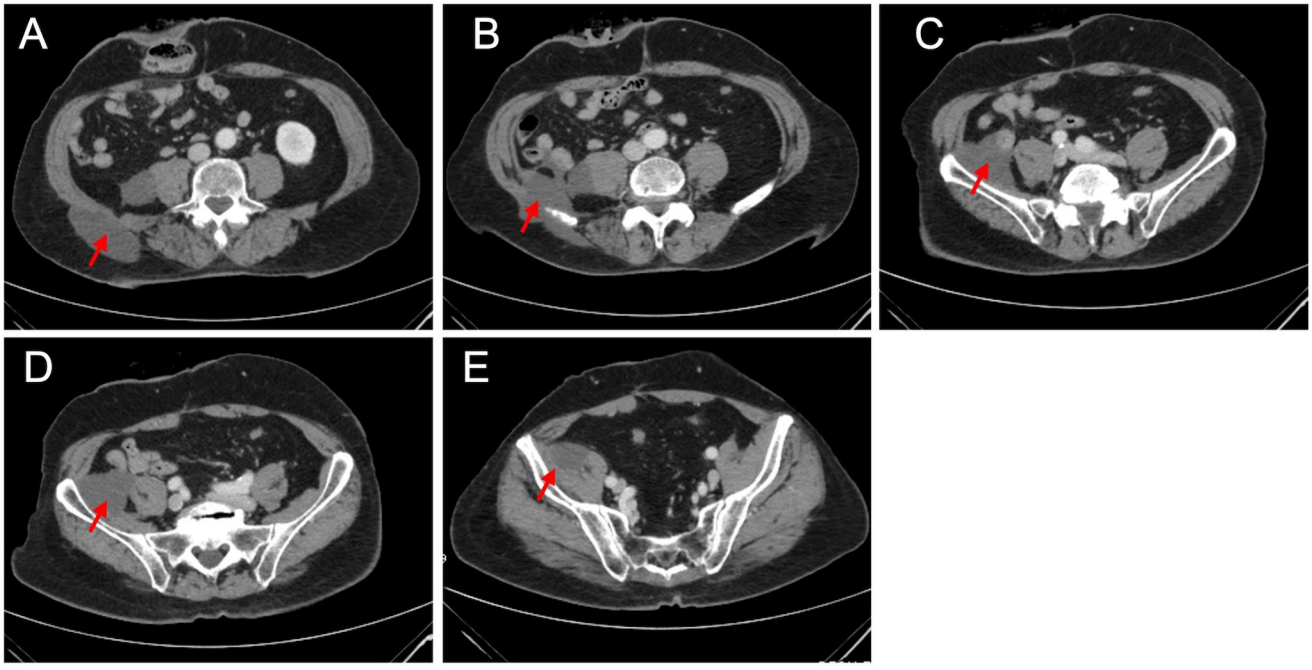

Figure 3 Axial CT sections showing improvement in right lower quadrant mass after 16 cycles of pembrolizumab and most recent follow-up.

over time. Had we moved him to hospice and strictly palliative care when he appeared to be progressing, he would not have received his third cycle of pembrolizumab and would have been at greater risk of true disease progression. The lack of diagnostic tools to promptly differentiate between true progression and pseudoprogression could have been detrimental to this patient had he not continued with therapy. The field lacks strategies capable of distinguishing true progression from pseudoprogression. New techniques are needed to avoid potentially harmful therapy alterations, prolongation of therapy and unnecessary transition to palliative care.

Currently, the diagnosis of pseudoprogression relies heavily on clinical judgement, which typically includes the observation of asymptomatic enlargement of the tumour. This clinical judgement can then be verified retrospectively when scans show improvement following continued ICI treatment. This retrospective verification is a limitation, as it prevents clinicians from accurately evaluating ICI efficacy in a timely manner. This places patients at risk as some require a switch in therapy for management of true progression, while others with pseudoprogression will benefit from continuation of immunotherapy. CT and MRI are the imaging modalities most commonly used to diagnose tumour progression; however, they have been insufficient in accurately differentiating true progression and pseudoprogression. One study demonstrated this limitation, as it found that 12 of 28 patients with pathologically confirmed pseudoprogression underwent unnecessary surgery risk due to misclassification of tumour progression by MRI.[29]

With the increasing rate of immunotherapy utilisation to treat patients with cancer, it is increasingly important to promptly and accurately differentiate between true progression and pseudoprogression. Lesion biopsies have shown variable promise in deducing the presence of pseudoprogression by detecting immune cells in place of the expected tumour cells, necessitating further follow-up with imaging. However, biopsies are limited because clinicians must rule out confounding variables such as infection and other causes of heightened immune cell infiltration. A biopsy only gives results for a single small area and may not reflect the entire tissue. Due to these conditions and the invasive nature of biopsies, other methods of pseudoprogression must be developed.[17]

One imaging modality that has shown some promise in interrogating immune responses for ICI is PET. PET imaging has been effective in detecting pseudoprogression in patients undergoing chemotherapy and radiotherapy,[30 31] and it may play a significant role in the future diagnosis of pseudoprogression following ICI treatment. A small retrospective study of fluorodeoxyglucose (FDG)-PET imaging showed significantly lower than expected levels of FDG uptake in pseudoprogressive masses when compared with truly progressing disease.[32] Though these results are promising, other studies have shown that this method of pseudoprogression detection is limited, and several other factors need to be considered, including variation in baseline metabolic activity and the heterogeneity in metabolic activity of various cancers.[17 33–35] US also has the potential to aid in the diagnosis of pseudoprogression. A 2017 case study on melanoma pseudoprogression found a 20% decrease in blood flow within pseudoprogressive tumours compared with baseline. According to this report, the use of Doppler US could lead to earlier detection of pseudoprogression in superficial tumours owing to the quantifiable blood flow decline within pseudoprogressive tumours.[35]

Novel imaging techniques are in development that may allow for more promising methods of diagnosing pseudoprogression. One such technique uses 4-[18F] fluoro-1-naphthol ([18F]4FN), which can be detected using PET imaging. This redox-tuned radiopharmaceutical allows for selective detection and observation of innate immunity. [18F]4FN selectively binds cells and proteins when oxidised by-products of human MPO and H2O2, which are commonly produced by active myeloid cell infiltrates.[36] Unlike other imaging modalities, [18F]4FN PET imaging would allow clinicians to non-invasively characterise a tumour's response to ICI by interrogating innate immune cell infiltrate to determine tumour or immune cell-driven pseudoprogression. Another approach would be direct radiolabelling of immune cells. Studies using PET imaging with probes specific for T-cells have shown that intratumoural and systemic immune alterations can be successfully monitored.[37–39] These techniques have the potential to be useful tools in diagnosing pseudoprogression. Other techniques that show promise include gadolinium contrast-enhanced MRI,[40] percent change of perfusion skewness and kurtosis,[41] ferumoxytol,[42] volume-weighted voxel-based multiparametric clustering,[43] parametric response map[44] and interval change in diffusion and perfusion MRI parameters,[45] which have all shown promise in diagnosing pseudoprogression in chemotherapy-treated patients.

In conclusion, this patient with high microsatellite instability and metastatic CRC initially presented with worsening clinical symptoms and scans concerning for disease progression. While he had only received two cycles of ICI, there was concern for true disease progression because of his symptomatic presentation and significant decline in performance status. Transitioning to hospice was briefly considered given the notable increase in tumour size; however, on follow-up after discharge, his symptoms significantly improved, as did his tumour markers. We ultimately made the decision to continue treatment with ICI. Clinical decisions such as these can be somewhat challenging, but they need to take precedence over complete reliance on imaging. Physicians must use their clinical judgement while considering the available physical examination findings and pertinent lab markers. With the increasing usage of immunotherapies to treat cancer, there is a dire need for more advanced diagnostic tools to differentiate between pseudoprogression and true progression. Lesion biopsies and conventional imaging modalities are limited in their diagnostic utility, and novel alternatives must be developed. Though promising results have been seen in retrospective studies, there remains an unmet need for non-invasive imaging techniques that will aid clinicians in characterising pseudoprogression to avoid harmful therapy alterations, therapy prolongation and unnecessary clinical transition to palliative care.

Learning points

- Pseudoprogression is conventionally defined as an increase in the size(s) of and/or visual appearance of new lesion(s), followed by a response.
- While rare, pseudoprogression can be accompanied by worsening clinical symptoms.
- To differentiate pseudoprogression from true progression, physicians should not rely solely on radiological findings and must use their clinical judgement while considering the available physical examination findings and pertinent lab markers.
- There is an increasing need for advanced, non-invasive imaging techniques to aid in the characterisation of pseudoprogression.

Patient'S perspective

I want to express my immense happiness and honesty in the effectiveness of my treatment and the discussion of my case. It is not just about the treatment itself; it is also about the invaluable assistance I have received from the doctors.

Moreover, for all those who have stood in solidarity with me, I would like to offer advice to individuals with similar cases to mine. I encourage them to embrace the treatment and maintain the same positive attitude that I have held—an attitude focused on overcoming cancer. Trusting the healthcare providers delivering the treatment is equally important. I believe that this case report can serve as a guiding light for other patients who can learn and benefit from this treatment. I want to stress the significance of placing trust both in the doctor and the medication. Without trust, progress becomes challenging. The patient–doctor relationship is a pivotal part of the healing journey. I was fortunate to have an exceptional doctor who earned my complete trust as we battled against cancer together.

Lastly, from my perspective, this endeavour necessitates a collaborative team effort involving the patient, treating doctor and the medical staff. When everyone works cohesively with a positive outlook and aptitude, success is undoubtedly within reach. Indeed, it will be.

Contributors KH, AAZ, NB, JW were responsible for drafting of the text, sourcing and editing of clinical images, investigation results, drawing original diagrams and algorithms, and critical revision for important intellectual content. KH, AAZ, NB, JW gave final approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD

Jason Willis http://orcid.org/0000-0001-8238-8552

REFERENCES

1 Siegel RL, Miller KD, Wagle NS, *et al*. Cancer Statistics. *CA A Cancer J Clinicians* 2023;73:17–48.
2 Valle L, Vilar E, Tavtigian SV, *et al*. Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. *J Pathol* 2019;247:574–88.
3 Barrow P, Khan M, Lalloo F, *et al*. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous Polyposis and Lynch syndrome. *Br J Surg* 2013;100:1719–31.
4 Møller P, Seppälä TT, Bernstein I, *et al*. Cancer risk and survival in Path_Mmr carriers by gene and gender up to 75 years of age: a report from the prospective Lynch syndrome database. *Gut* 2018;67:1306–16.
5 Therkildsen C, Ladelund S, Smith-Hansen L, *et al*. Towards Gene- and gender-based risk estimates in Lynch syndrome; age-specific incidences for 13 extra-colorectal cancer types. *Br J Cancer* 2017;117:1702–10.
6 Lynch HT, Snyder CL, Shaw TG, *et al*. Milestones of Lynch syndrome: 1895–2015. *Nat Rev Cancer* 2015;15:181–94.
7 Kloor M, Becker C, Benner A, *et al*. Immunoselective pressure and human Leukocyte antigen class I antigen machinery defects in Microsatellite unstable colorectal cancers. *Cancer Res* 2005;65:6418–24.
8 Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. *Nat Rev Immunol* 2015;15:486–99.
9 Therkildsen C, Jensen LH, Rasmussen M, *et al*. An update on immune Checkpoint therapy for the treatment of Lynch syndrome. *Clin Exp Gastroenterol* 2021;14:181–97.
10 Alsaab HO, Sau S, Alzhrani R, *et al*. PD-1 and PD-L1 Checkpoint signaling inhibition for cancer Immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol* 2017;8:561.
11 Brahmer JR, Tykodi SS, Chow LQM, *et al*. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455–65.
12 Santoni M, Montironi R, Battelli N, *et al*. Hans hammers, and Daniel George's letter to the editor re: Arnaud Mejean, Alain Ravaud, Simon Thezenas, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. Eur Urol 2018;74:842-3: lymphocyte phenotype and timing of radical nephrectomy in patients treated with Immunocheckpoint inhibitors for renal cell carcinoma. *Eur Urol* 2019;75:e64–6.
13 Topalian SL, Hodi FS, Brahmer JR, *et al*. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54.
14 Buchbinder E, Hodi FS. Cytotoxic T lymphocyte Antigen-4 and immune Checkpoint blockade. *J Clin Invest* 2015;125:3377–83.
15 Kwak JJ, Tirumani SH, Van den Abbeele AD, *et al*. Cancer Immunotherapy: imaging assessment of novel treatment response patterns and immune-related adverse events. *Radiographics* 2015;35:424–37.
16 Di Giacomo AM, Danielli R, Guidoboni M, *et al*. Therapeutic efficacy of Ipilimumab, an anti-CTLA-4 Monoclonal antibody, in patients with metastatic Melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer Immunol Immunother* 2009;58:1297–306.
17 Ma Y, Wang Q, Dong Q, *et al*. How to differentiate Pseudoprogression from true progression in cancer patients treated with Immunotherapy. *Am J Cancer Res* 2019;9:1546–53.
18 Jia W, Gao Q, Han A, *et al*. The potential mechanism, recognition and clinical significance of tumor Pseudoprogression after Immunotherapy. *Cancer Biol Med* 2019;16:655–70.
19 Tanizaki J, Hayashi H, Kimura M, *et al*. Report of two cases of Pseudoprogression in patients with non-small cell lung cancer treated with Nivolumab-including histological analysis of one case after tumor regression. *Lung Cancer* 2016;102:44–8.
20 Hodi FS, Hwu W-J, Kefford R, *et al*. Evaluation of immune-related response criteria and RECIST V1.1 in patients with advanced Melanoma treated with Pembrolizumab. *J Clin Oncol* 2016;34:1510–7.
21 Queirolo P, Spagnolo F. Atypical responses in patients with advanced Melanoma, lung cancer, renal-cell carcinoma and other solid tumors treated with anti-PD-1 drugs: A systematic review. *Cancer Treat Rev* 2017;59:71–8.
22 Wolchok JD, Hoos A, O'Day S, *et al*. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412–20.
23 Thomas R, Somarouthu B, Alessandrino F, *et al*. Atypical response patterns in patients treated with Nivolumab. *AJR Am J Roentgenol* 2019;212:1177–81.
24 Seymour L, Bogaerts J, Perrone A, *et al*. iRECIST: guidelines for response criteria for use in trials testing Immunotherapeutics. *Lancet Oncol* 2017;18:e143–52.
25 Pignon J-C, Jegede O, Shukla SA, *et al*. irRECIST for the evaluation of candidate biomarkers of response to Nivolumab in metastatic clear cell renal cell carcinoma: analysis of a phase II prospective clinical trial. *Clin Cancer Res* 2019;25:2174–84.
26 Persigehl T, Lennartz S, Schwartz LH. iRECIST: how to do it. *Cancer Imaging* 2020;20:2.
27 Champiat S, Ferrara R, Massard C, *et al*. Hyperprogressive disease: recognizing a novel pattern to improve patient management. *Nat Rev Clin Oncol* 2018;15:748–62.
28 André T, Shiu K-K, Kim TW, *et al*. Pembrolizumab in Microsatellite-instability-high advanced colorectal cancer. *N Engl J Med* 2020;383:2207–18.
29 Topkan E, Topuk S, Oymak E, *et al*. Pseudoprogression in patients with glioblastoma multiforme after concurrent radiotherapy and Temozolomide. *Am J Clin Oncol* 2012;35:284–9.
30 Galldiks N, Dunkl V, Stoffels G, *et al*. Diagnosis of Pseudoprogression in patients with glioblastoma using O-(2-[18F]Fluoroethyl)-L-tyrosine PET. *Eur J Nucl Med Mol Imaging* 2015;42:685–95.
31 Kebir S, Fimmers R, Galldiks N, *et al*. Late Pseudoprogression in glioblastoma: diagnostic value of dynamic O-(2-[18F]Fluoroethyl)-L-tyrosine PET. *Clin Cancer Res* 2016;22:2190–6.
32 Kebir S, Rauschenbach L, Galldiks N, *et al*. Dynamic O-(2-[18F]Fluoroethyl)-L-tyrosine PET imaging for the detection of Checkpoint inhibitor-related Pseudoprogression in Melanoma brain metastases. *Neuro Oncol* 2016;18:1462–4.
33 Costa LB, Queiroz MA, Barbosa F de G, *et al*. Pseudoprogression on PSMA PET imaging of a mCRPC patient under anti-Pd1 treatment. *Eur J Nucl Med Mol Imaging* 2019;46:1576–7.
34 Imafuku K, Hata H, Kitamura S, *et al*. "Ultrasonographic findings can identify 'Pseudoprogression' under Nivolumab therapy". *Br J Dermatol* 2017;177:1726–31.

35 Sachpekidis C, Larribere L, Pan L, *et al*. Predictive value of early 18F-FDG PET/CT studies for treatment response evaluation to Ipilimumab in metastatic Melanoma: preliminary results of an ongoing study. *Eur J Nucl Med Mol Imaging* 2015;42:386–96.
36 Pisaneschi F, Gammon ST, Paolillo V, *et al*. Imaging of innate immunity activation in vivo with a redox-tuned PET reporter. *Nat Biotechnol* 2022;40:965–73.
37 Wei W, Jiang D, Ehlerding EB, *et al*. Noninvasive PET imaging of T cells. *Trends Cancer* 2018;4:359–73.
38 Lu D, Wang Y, Zhang T, *et al*. Metabolic Radiolabeling and in vivo PET imaging of cytotoxic T lymphocytes to guide combination adoptive cell transfer cancer therapy. *J Nanobiotechnology* 2021;19:175.
39 Moroz MA, Zanzonico P, Lee JT, *et al*. Ex vivo Radiolabeling and in vivo PET imaging of T cells expressing nuclear reporter genes. *Methods Mol Biol* 2018;1790:153–63.
40 Barajas RF, Hamilton BE, Schwartz D, *et al*. Combined iron oxide nanoparticle Ferumoxytol and Gadolinium contrast enhanced MRI define glioblastoma Pseudoprogression. *Neuro Oncol* 2019;21:517–26.
41 Baek HJ, Kim HS, Kim N, *et al*. Percent change of perfusion Skewness and Kurtosis: a potential imaging biomarker for early treatment response in patients with newly diagnosed Glioblastomas. *Radiology* 2012;264:834–43.
42 Gahramanov S, Muldoon LL, Varallyay CG, *et al*. Pseudoprogression of glioblastoma after Chemo- and radiation therapy: diagnosis by using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging with Ferumoxytol versus Gadoteridol and correlation with survival. *Radiology* 2013;266:842–52.
43 Park JE, Kim HS, Goh MJ, *et al*. Pseudoprogression in patients with glioblastoma: assessment by using volume-weighted Voxel-based Multiparametric clustering of MR imaging data in an independent test set. *Radiology* 2015;275:792–802.
44 Tsien C, Galbán CJ, Chenevert TL, *et al*. Parametric response map as an imaging biomarker to distinguish progression from Pseudoprogression in high-grade glioma. *J Clin Oncol* 2010;28:2293–9.
45 Knitter JR, Erly WK, Stea BD, *et al*. Interval change in diffusion and perfusion MRI parameters for the assessment of Pseudoprogression in cerebral metastases treated with stereotactic radiation. *AJR Am J Roentgenol* 2018;211:168–75.