Q1 がん薬物療法のマネジメントはなぜ必要か

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point

- がん薬物療法の進歩により，以前よりがん薬物療法のマネジメントが大事になっている．
- 医療機関や医療従事者がさまざまな形でマネジメントを行う必要がある．
- 患者や家族への教育がマネジメントに必要なこともある．
- 医師，薬剤師，看護師が個人で対応するだけでは不十分である．
- 同じ職種内や多職種間のチーム医療が必要．
- 医療機関の体制や設備の整備，専門性の向上，標準化および患者の啓発の視点が必要である．

Q がん薬物療法のマネジメントはなぜ必要なのですか？

A 最近のがん薬物療法の進歩には目覚ましいものがあり，分子標的治療薬などの抗がん剤や制吐などの支持療法薬の種類の増加，適応症の拡大，治療を受ける患者数の増加，治療期間の延長とともに，治療を行う医療機関や医師の数も増えています．治療の選択肢が増える一方で，日常診療では治療の適応や治療の選択に迷うことも少なくありません．また，最近のがん薬物療法は外来で行われる場合が多く，内服薬のコンプライアンスの向上や副作用に関する患者教育が必要になってきました．

患者に最適な治療を選択し，効果を最大限に引き出し，しかも安全に投与することは決して容易ではありません．まず，治療を担当する医師の専門性が問われます．しかし，治療適応，有効で安全な治療を行うことは一人の専門医だけでは実現しません．治療に携わる看護師や薬剤師の専門性を高め，チーム医療としてがんの薬物療法を行う体制の整備が医療機関に求められています．

Q がん薬物療法のマネジメントがうまくいかないと，どのような問題が起きますか？

A 患者に最適な治療を選択できない，医師によって治療の種類，用法・用量が異なるなど，質の高い治療を提供できなくなります．このようなことは患者にとって大き

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な不利益です．これまでに医師の指示のうっかりミスや調剤ミスで過剰投与による事故が起きたケースは少なくありません．死亡事故に至ったケースもあります．薬剤師および看護師が治療内容を理解し，医師の処方・指示内容を二重，三重にチェックできれば防げた医療事故もあります．医師に薬物相互作用に関する知識がないために起きた死亡事故もあります．このような事故は薬剤師による処方監査体制があれば防止できた可能性があります．内服薬の場合は，患者の誤用により過剰投与になる場合があります．患者教育は明らかに必要です．逆に，副作用が少なくなるからという医師の誤った考え方により，過少投与になる場合がしばしば見受けられます．過少投与は治療効果を減じる可能性が高いと考えるべきです．また，副作用に対する支持療法がうまく行われないと患者のQOLが低下し，本来なら有効な治療が中止，減量または延期になる場合があります．さらに，外来化学療法室でアナフィラキシーショックやインフュージョンリアクションなどの重篤な副作用が発症した場合，医師や現場の看護師が迅速に適切な対応ができなければ患者の生死に関わります．

Q がん薬物療法のマネジメントに必要なことは何ですか？

A がん薬物療法のマネジメントには，大きく分けて4つあります．第一は医療機関の体制や設備の整備です．第二は医療従事者の専門性の向上です．第三は治療内容の標準化です．第四は患者の啓発です．この4項目は相互に関係があり，すべてを強化しておくことが質の高いがん薬物療法の提供には効果的です．医療機関の体制整備には，都道府県や地域（二次医療圏）のがん診療連携拠点病院の機能整備（指定要件の整備），外来化学療法室の施設，設備や運営体制の整備が必要です．医師，薬剤師および看護師による処方・指示内容の二重，三重チェック，薬剤師による処方監査，アナフィラキシーショック時のシミュレーション訓練の定期的実施など，医療機関がチーム医療を実施できる体制を構築しておく必要があります．医療従事者の専門性を向上するには，院内勉強会の開催による医療従事者の啓発，関連学会への参加，臨床研究の推進と学会での発表，がん薬物療法専門医などの専門医療者（表1）の資格取得率の向上が必要です．

治療内容の標準化については，レジメン審査委員会による治療内容の評価やレジメン登録制の導入，診療科内症例検討会や診療科横断的症例検討会による治療の最適化，治療を標準化して実行するためのクリニカルパスの導入やメディカルIT，治療内容だけでなく副作用のマネジメントの標準化のために必要ながん診療ガイドラインの適応，などが挙げられます．患者の啓発は，がん薬物療法が外来中心に行われるようになった今日ではたいへん重要です．専門的な治療や副作用に関することを患者に理解してもらうのは容易ではありません．予測される副作用に関して教材を用いて事前に説明し，健康管理手帳を渡して副作用の発現状況を記載してもらう必要があります．このような患者教育は医師だけでなく，看護師や薬剤師が参加したチームにより協同で，時には役割分担して行うのが効果的です．最近では，抗がん剤の薬価が高額なため，治療の前に，患者や家族に予想される

表1　がん薬物療法のマネジメントに必要なこと

項　目	具体的な項目
医療機関の体制や設備の整備	がん診療連携拠点病院としての機能，外来化学療法室の設備や運営体制の整備，スタッフの専任化，医師，薬剤師および看護師による処方・指示内容の二重，三重チェック，薬剤師による処方監査，アナフィラキシーショック時のシミュレーション訓練の定期的実施，救急外来との連携，病診連携の構築など
医療従事者の専門性の向上	がん薬物療法専門医，がん看護認定看護師，がん化学療法看護認定看護師，がん専門薬剤師，がん薬物療法認定薬剤師など専門資格取得，院内勉強会の開催，研究推進と学会参加と発表など
治療内容の標準化	レジメン審査委員会，レジメン登録制，診療科内症例検討会，診療科横断的症例検討会，クリニカルパスの導入，メディカルIT，ガイドラインの適応，副作用のマネジメント，救急処置の対応マニュアル作成など
患者（ときに家族）の啓発	チーム医療による（時に職種別）の患者教育，患者教育ツール作成，治療内容（効果だけでなく，服薬の仕方，副作用に対する対処）のわかりやすい説明，相談窓口の設置など

医療費や高額療養費制度について説明しておくことが必要です．その際，医療ソーシャルワーカー（MSW）にこの説明業務を分担しておくと，患者や家族の理解がより深まるほか，医師や看護師の本来の業務を円滑に進めるうえで有用です．

Q　がん薬物療法のマネジメントの最近の動向は？

A　分子標的治療薬が数多く登場し，副作用が多様化しています．血管新生阻害薬による血栓塞栓症，消化管穿孔，高血圧症，創傷治癒遅延にタンパク質尿，抗EGFR抗体薬やEGFR-TKI（tyrosine kinase inhibitor）による多様な皮膚障害，抗体薬によるインフュージョンリアクションなど，従来の化学療法剤とは異なる副作用がみられます．このため，個々の副作用に対する支持療法のほかに，循環器内科，消化器外科，皮膚科などの専門診療科との連携が必要になっています．一方，マネジメントを効率的に行うための標準化が必要ですが，がん薬物療法がバイオマーカーの導入により個別化の報告に向かっています．このため，がん薬物療法のマネジメントは今後より複雑化する可能性があります．また，外来で治療を受ける患者が大部分であるため，救急外来など時間外の対応を構築しておく必要があります．さらに，がん診療の地域連携の必要性から，地域の医療機関との病診連携や病々連携が必要な場合も生じてきました．

Q　がん薬物療法のマネジメントは誰が行うのですか？

A　ここまで読まれた方はすでにお気づきのとおり，がん薬物療法に関わるあらゆる職種，立場の方にマネジメントが求められます．医師なら，病院長，関連する診療科

長，医長，主治医，外来化学療法室長，看護師なら看護部長，関連する看護師長，担当する看護師，外来化学療法室の専任看護師，薬剤師なら，薬剤部長，抗がん剤の調剤担当薬剤師，処方監査担当薬剤師，外来化学療法室の専任薬剤師など多くの立場の医療従事者が関与する必要があります．また，時には患者やその家族がマネジメントに協力する必要があります．特に重要なのは，がん薬物療法の専門性が高い，例えばがん薬物療法専門医の腫瘍内科医に院内のがん薬物療法のマネジメントを系統的に行うように権限を与えて，がん専門薬剤師やがん化学療法認定看護師らとともに上記の実現を図ることが質の高い治療をより安全に患者に提供するために必要です．

《総論》

1 最新のがん薬物療法の特徴と適応

石岡千加史*
いしおかちかし

ポイント

- 新規抗がん剤の多くは分子標的治療薬であり，さまざまながん腫で治療成績の向上がもたらされた．
- 抗がん剤治療の適応に際し，がんの状態，宿主（患者）の心身状態，社会的要因を考慮する必要がある．
- 適応決定に必要ながんの状態としては，がんの種類，臨床病期（周術期治療か進行・再発癌か），病理組織学的分類がある．
- 適応決定に必要な宿主（患者）側の要因として宿主の全身状態，主要臓器機能，年齢や社会的な要因がある．
- 最近は，抗がん剤治療の適応や効果予測のためのバイオマーカーが導入されている．

キーワード 分子標的治療薬，抗がん剤の適応，RECIST，CTCAE

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◉最新のがん薬物療法の特徴

21世紀に入りがん薬物療法の主役は化学療法薬から分子標的治療薬に変わった．過去10年間に新たに承認された抗がん剤の多くは分子標的治療薬である．分子標的治療薬の登場により，これまで有効な薬剤がなかったがん腫や，化学療法薬に抵抗性になったがんへ新規の適応や適応拡大が進んでいる．一方，1963年に東ドイツで作られた化学療法薬ベンダムスチンは悪性リンパ腫に対して有効であることが示され，最近になって米国や日本で承認された例もある．新薬の登場により，さまざまながん腫で治療成績の向上が得られているが，これまでの抗がん剤にみられなかった副作用の問題や治療薬が高額であることの問題が生じている．

◉最新のがん薬物療法の適応

最近，がん薬物療法の進歩は目覚ましいが，治療効果や副作用の点において未だ発展途上である．このため，がん薬物療法の実施にあたっては個々の薬剤の知識，併用療法の効果と副作用に関する知識はもとより，患者のがん種，病理組織型，バイオマーカー，臨床病期，全身状態，主要臓器予備能，既往歴や合併疾患など，その適応にあたって十分な専門性が求められる．また，一度治療を開始した場合，治療継続，中止，延期，減量をどのように客観的に判断するのか，基本的な知識を身につける必要がある．

◉抗がん剤治療の適応決定と目標

抗がん剤治療を適応する際には原則として，(1) がんの種類と臨床病期の診断，(2) 治療時期（1次治療か2次治療か）に対応した標準治療の有無，(3) 患者の全身状態 Performance Status，(4) 主要臓器機能と合併症の評価，(5) インフォームド・コンセント（IC）が必要である．ICに際しては，病名，病状の説明に加えて，期

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表 1　抗がん剤治療の目標

抗がん剤単独で治癒が期待できるがん
長期無病生存，長期無病生存率の向上 例：白血病，悪性リンパ腫，胚細胞腫瘍など
補助化学療法で再発抑制が期待できるがん
無再発，無再発期間や全生存期間の延長 例：乳癌，胃癌，大腸癌など
切除不能進行または再発がんで延命効果が期待できるがん
無増悪，無増悪生存期間や全生存期間の延長 例：乳癌，大腸癌など
延命効果は小さいが症状改善が期待できるがん
症状緩和などQOLの向上 例：膵癌など

表 2　投与可能，休薬，中止，減量の判断基準

投与可能基準	投与直前の血液または非血液毒性が無い，または軽微であること（たとえばNCI-CTCAE ver 4のグレード1以下）
休薬基準	投与可能基準を上回る中等度以上の有害事象であるが，延期により投与再開が許容できること
中止基準	回復が見込まれないか，生命の危険性がある重篤な有害事象があること
減量基準	前回治療から投与直前までに高度の毒性（たとえばグレード4の血液毒性またはグレード3以上の非血液毒性）が認められた場合に薬剤を一定（たとえば20%）の割合で段階的に減量

待される治療効果と予想される副作用，治療期間，入院か通院か，費用や高額療養費制度などの説明と文書による同意取得が必要である．抗がん剤治療の目標は治癒，延命，再発抑制またはQOLの向上があり，がんの種類，臨床病期によって異なる（**表1**）．

◉治療効果の評価と腫瘍縮小効果

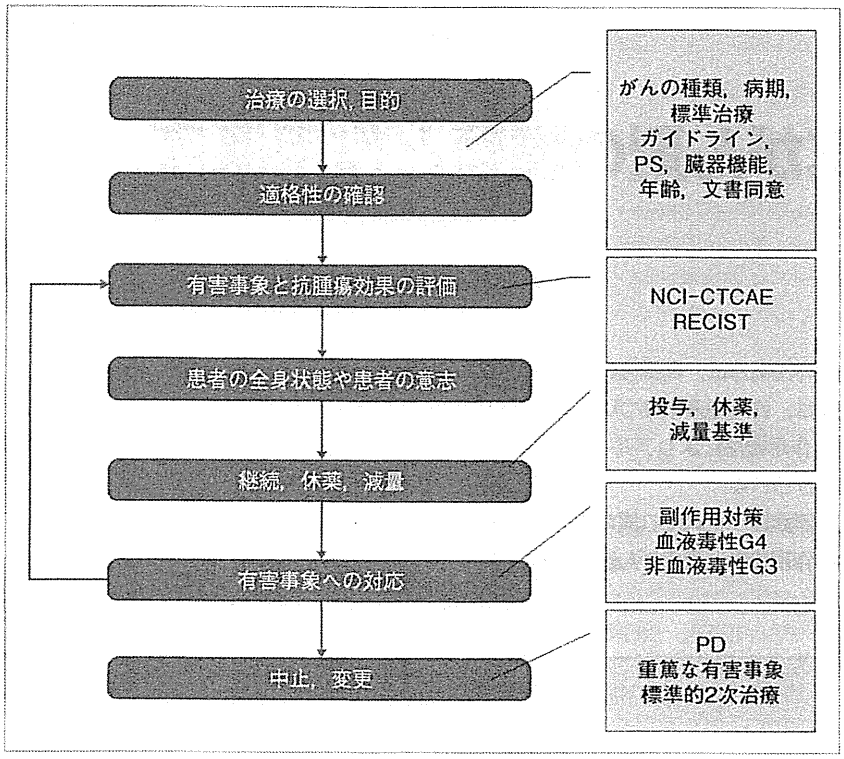
検証的臨床試験（多くは無作為比較試験）の1次エンドポイントは，切除不能進行・再発がんの場合は全生存期間や無増悪生存期間，術後補助科学療法や造血器腫瘍の場合は無再発生存期間や無病生存期間である．一般的に固形がんの多くは治療効果が不確実であり，日常診療において患者の治療継続の判断には副作用の評価（後述）のほか，継続投与により治療効果（生存期間の延長）が得られるか一定治療期間毎（たとえば2ヵ月毎）に評価する必要がある．固形がんの場合は，生存期間のサロゲートマーカーとして腫瘍縮小を指標にしたRECISTガイドライン[1]が客観的効果判定基準として用いられている．これは臨床試験のための国際的判定基準であるが，がんの日常診療において臨床医が客観的に治療継続の可否を決定するための指標として用いられている．

◉副作用の評価

がん薬物療法の副作用は他の疾患の薬物療法と比較すると，多様で高頻度である．このため，副作用の評価とマネジメントは治療の継続のために重要である．副作用の評価には，臨床試験で汎用される有害事象の評価基準Common Terminology Criteria for Adverse Events（CTCAE）v4.0[2]が用いられる．臨床試験や治験に参加しない日常診療においては，CTCAEによる厳密な副作用の記載は必要ないが，治療の継続，中止，減量や延期の判断，副作用のマネジメント，他施設への紹介の際の医療従事者間の情報交換，後ろ向き臨床研究における副作用の評価など，日頃からCTCAEに準拠した副作用の記載を心がけるべきである．

◉投与量・投与スケジュールの決定

がん薬物療法における標準治療とは，信頼できる検証的臨床試験において従来の標準治療との比較試験により，効果や安全性が同等以上であることが検証されている治療であり，学会等の専門家コミュニティにおいて日常診療での使用が推奨される治療を指す．具体的な治療については，国内の学会等が作成する各種がん診療ガイドラインに記載されている．また，がん診療ガイドラインの簡易版の多くは日本癌治療学会のホームページか



（石岡千加史，井上忠夫 編：エビデンスに基づいたがん薬物療法エキスパートマニュアル．総合医学社，東京，2012より引用）

図 1 **抗がん剤治療実施の流れ**
抗がん剤治療を適応する際に治療の各段階で考慮すべき事項を示す．

ら閲覧できる[3]．また，海外のガイドラインとして，NCCN ガイドライン[4]や ASCO ガイドライン[5]が参考になるが，わが国の保険診療の枠組みのなかで使用する場合は，適応症，用法および用量に関して適応外使用になる場合があり，注意を要する．

◉投与可能，休薬，中止，減量の判断

投与可能の判断や，副作用が出現した場合の休薬，中止，再開や減量の判断についても臨床試験で行われた方法に準拠するのが望ましい．一般的な投与可能，休薬，中止，減量の判断基準を**表 2** に示す．

患者に対してより効果が期待できる治療を安全に提供するためには，がん薬物療法専門医のような高い専門性が求められている．抗がん剤治療を適応する際に考慮すべき事項をフローチャートにまとめた（**図 1**）．抗がん剤治療の原則は，最新の科学的（医学的）根拠に基づき標準治療を選択することである．新しい標準治療の導入に躊躇し，「過去の標準治療」を継続することは患者にとって不利益である．がん治療を行う医療従事者として常にガイドライン，論文や学会活動を通じて新しい標準治療を取り入れる必要がある．

文 献

1) Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer**45**(2): 228-247, 2009
2) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40)
3) 日本癌治療学会 がん診療ガイドライン (http://www.jsco-cpg.jp/)
4) NCCN ガイドライン (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)
5) ASCO ガイドライン (http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Clinical+Practice+Guidelines)

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Multidisciplinary approach to a case of Lynch syndrome with colorectal, ovarian, and metastatic liver carcinomas

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Abstract Lynch syndrome is an autosomal dominant disorder with an estimated prevalence of 3 % of all colorectal cancers. It is attributed to germline mutations in DNA mismatch repair (MMR) genes, which confer increased susceptibility to cancers of the colorectum, endometrium, stomach, small intestine, hepatobiliary system, kidney, urinary bladder, brain, and ovary. We report a thought-provoking Lynch syndrome case with a family history and simultaneous tumors in the colon, pelvis, and liver. These findings made diagnosis and treatment complicated. However, the multidisciplinary approaches followed by a medical oncologist, gynecologist, surgeon, radiologist, and pathologist led to a favorable outcome. This patient had two primary cancers of the colon and ovary, and systemic metastases of colon cancer. The loss of MSH6 protein expression was proven by immunohistochemical examination, but the germline *MSH6* mutation was not detected by DNA sequence analysis. Regarding this discrepancy, some possibilities, e.g., genomic rearrangements and epigenetic modifications, which can be missed by conventional sequence analysis, were considered. Theoretically, Lynch syndrome cases with MSH6 impairment exhibit late onset and low penetrance compared to other major cases with *MLH1* or *MSH6* mutations. Irinotecan hydrochloride (CPT-11) has favorable effects on MMR-deficient tumor cells with high microsatellite instability, although its clinical benefit remains controversial. In this case, the first-line chemotherapy bevacizumab + FOLFIRI regimen has been effective for over a year in the partial response state. We discuss the diagnostic, therapeutic, pathological, and molecular biological characteristics of this intriguing case, indicating the importance of family history, histological assessment, and molecular biological etiology in Lynch syndrome cases presenting a complicated phenotype.

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Keywords Lynch syndrome · Family history · *MSH6* · Irinotecan (CPT-11) · Multiple cancers

Case presentation

Dr. Ishioka (medical oncologist, chairperson of the conference): Good evening, everyone. Today, we would like to discuss a thought-provoking Lynch syndrome case. (*A brief summary of the case is given in the Abstract*). Dr. Shiono, please begin the case presentation.

Dr. Shiono (medical oncologist, physician in charge of this case): A 51-year-old woman, diagnosed with advanced colon cancer with multiple liver metastases, was referred to our outpatient department by her primary practitioner for systemic chemotherapy.

The patient had been well until 3 weeks before a visit to her doctor for right upper quadrant pain. Abdominal ultrasound revealed multiple masses in the liver. Subsequent computed tomography (CT) revealed metastases from an unknown origin (Fig. 1a), and a pelvic mass was considered as a right ovarian mucinous cystadenoma (Fig. 1b). While esophagogastroduodenoscopy (EGD) detected no lesions, colonoscopy disclosed a type 2 tumor in the sigmoid colon, which was histologically diagnosed as a poorly differentiated adenocarcinoma (Fig. 1c). There was nothing in particular to declare in the patient's past medical and social histories. She had never been married or pregnant, and was post-menopausal. Her family history revealed a background of Lynch syndrome. Her father had been diagnosed with colorectal cancer at the age of 42, and her two paternal uncles, aunt, and grandmother also had colorectal cancer (Fig. 2). This patient was diagnosed with Lynch syndrome by fulfilling the Amsterdam criteria II [1]. No apparent abnormalities were observed on physical examination. Laboratory data showed anemia (Hb 8.9 g/dl) and elevated CEA (1480 ng/ml) and CA19-9 (2418 U/ml) levels.

Differential diagnosis

To identify potential genes for Lynch syndrome, we submitted a colon cancer biopsy specimen for immunohistochemical (IHC) examination of the DNA mismatch repair (MMR) gene products, i.e., MLH1, MSH2, MSH6, and PMS2. Because Lynch syndrome was diagnosed, we could not completely rule out the possibility of ovarian cancer. An effective chemotherapy regimen should be selected based on the origin of the liver metastases. Hence, we consulted a radiologist and gynecologist for differential diagnoses of the pelvic tumor.

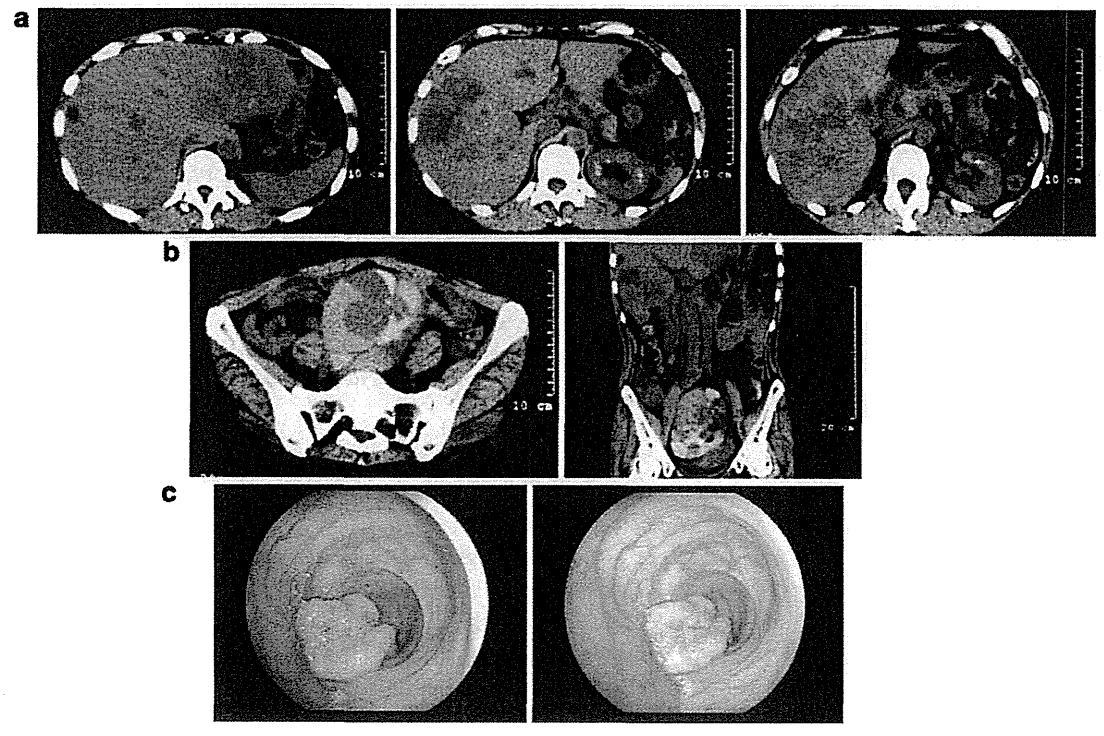


Fig. 1 CT images and colonoscopy findings at onset. **a** Axial images of the liver. Multiple low-density areas suggest metastases. **b** Axial and coronal images of the pelvic tumor. Various densities ranging from low to high, suggesting various liquid and solid components, are seen. **c** Captured images during colonoscopy. A massive type 2 tumor is seen in the sigmoid colon

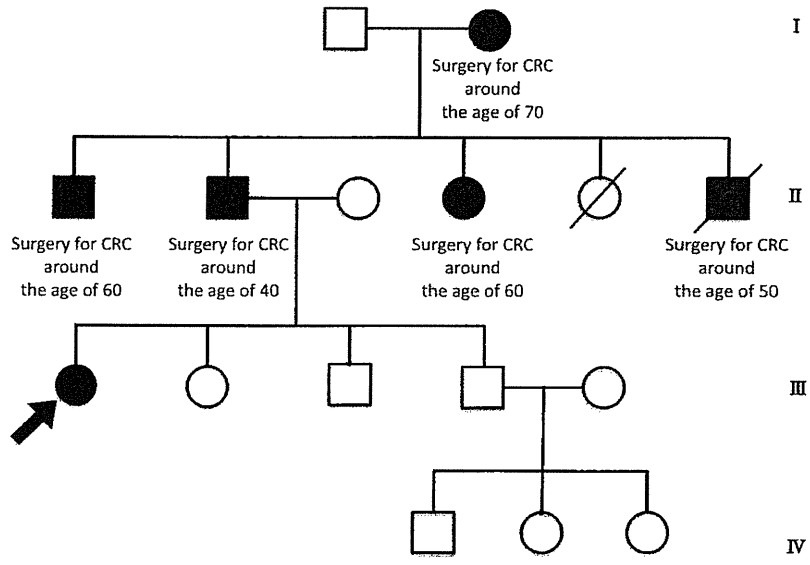


Fig. 2 Family tree. Five people were affected with colorectal cancer in the first degree relatives of the patient's father among three generations. Lynch syndrome was diagnosed, which fully met the diagnostic criteria of Amsterdam II. *Squares* and *circles* indicate male and female, respectively. *Arrow* indicates the patient. *Filling with black* indicates affected person with trait. *Diagonal line* indicates deceased relatives. *CRC* colorectal cancer

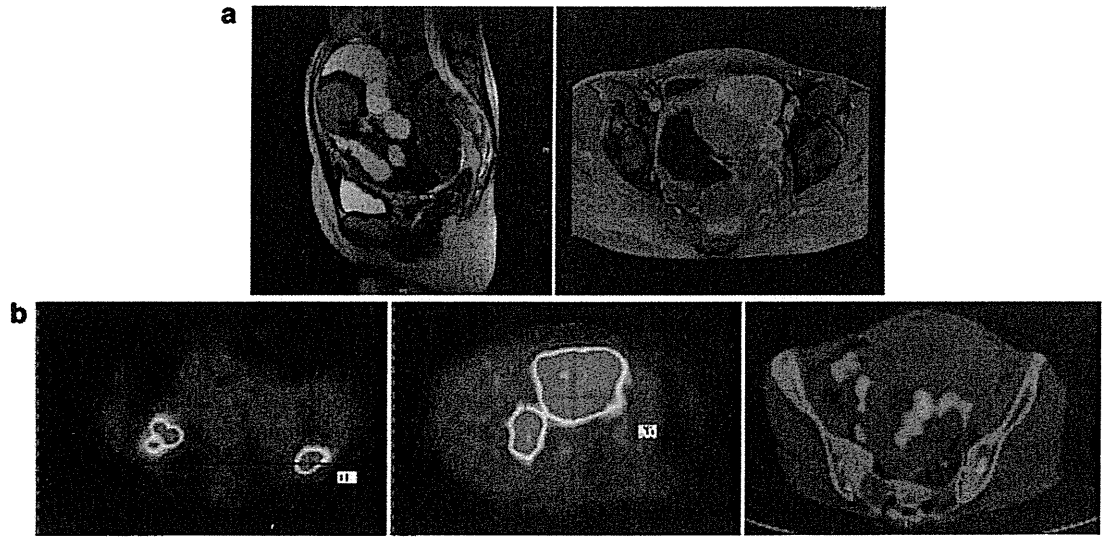


Fig. 3 PET–CT and MRI images 1 month after onset. **a** MRI images of the pelvic tumor. Mixtures of diverse intensities ranging from low to high, suggesting a variety of liquid and solid components, are seen. There seems to be a hemorrhage and mucus in it. Strong enhancement is seen in the cyst wall. A multilocular cystic ovary including a metastatic lesion of cyst walls with contrast enhancement was possibly suggested. **b** Axial PET–CT fusion images of the colon, liver, and ovary. SUV_{max} values of 9.0 in the colon, 7–10.0 in the liver, and 4.0 in the ovary were detected

Dr. Takase (*radiologist*): The pelvic mass was a multilocular cystic tumor, which showed various signals and densities on magnetic resonance imaging (MRI) and CT, respectively, presumably from a hemorrhage and mucus (Fig. 3a, left). Strong enhancement was observed in the cyst wall on MRI, although the solid part was minimal (Fig. 3a, right). A positron emission tomography/CT (PET–CT) image showed various maximum standardized uptake values showing malignancy (SUV_{max} 9.0 in the colon, 7.0–10.0 in the liver, and 4.0 in the ovary) (Fig. 3b). It is difficult to determine whether an ovarian tumor is primary or metastatic when another definitive tumor is apparent [2, 3]. Most metastatic ovarian tumors show solid and cystic components, but a cyst is not evidence of primary ovarian cancer. Unlike metastatic tumors of other organs, it is common for metastatic ovarian tumors to contain cysts even if the primary site solely consists of a solid mass. When an ovarian cystic tumor and primary cancer are observed simultaneously, we first consider the possibility of a metastatic ovarian tumor. However, it was quite difficult to distinguish the masses through imaging. We thought that this might be a multilocular cystic ovary

with metastatic lesions of the cyst walls with contrast enhancement [4].

Dr. Ito (gynecologist): Because few solid parts were present, which is often the case with primary ovarian cancer, in addition to normal CA-125 levels, a borderline tumor was conceivable in this case. However, laparotomy and histopathological assessment were necessary for the definitive diagnosis.

Initial treatment plan and its course

Dr. Shiono: Given the patient's history, we decided to prioritize chemotherapy for colorectal cancer, which had already been diagnosed as malignant. Considering her Lynch syndrome background, we selected an irinotecan hydrochloride (CPT-11)-based bevacizumab + FOLFIRI regimen. After confirming the uridine-5′-diphosphate-glucuronosyltransferase 1A1 (UGT1A1) *6 and *28 status as wild type for CPT-11 use, she was admitted for central venous port implantation for outpatient chemotherapy.

Because we used the biopsy specimens for MMR IHC, we performed colonoscopy to obtain biopsy samples for *KRAS* gene mutation analysis.

Dr. S. Takahashi (medical oncologist, operator of colonoscopy): Compared to the photograph taken by the former endoscopist 2 months earlier, the tumor had grown so rapidly that the lumen was subtotally occluded (Fig. 4a). Taken together with the fact that colon-cleaning preparation required considerable time, stenosis seemed to be severe. After acquiring the biopsy specimen, we performed CT to assess the indication for preemptive surgery for preventing mechanical colonic obstruction by the tumor.

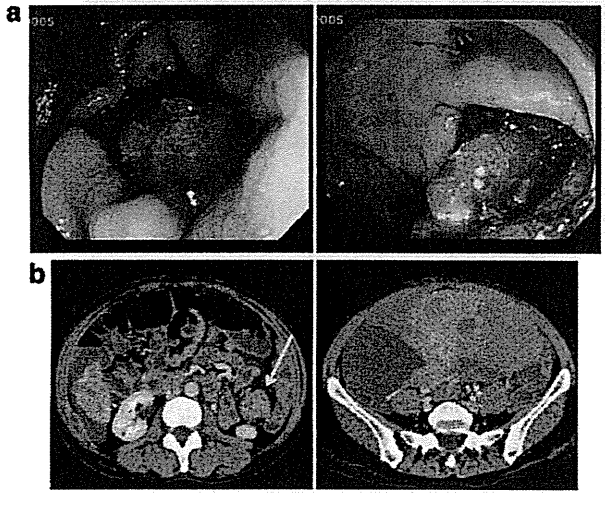


Fig. 4 Colonoscopy and CT images 2 months after onset. **a** Captured images during colonoscopy. Compared with Fig. 1c, the tumor had grown so rapidly that the lumen was subtotally occluded. **b** CT images of the colon and pelvic tumors. *Left panel* Upper colon from the stenosis site at the sigmoid with a massive tumor is enlarged. *Arrow* indicates the lesion. *Right panel* Pelvic tumor is also extremely increased in size compared with that in the former images

Dr. Takase: The upper colon from the stenosis site at the sigmoid with massive tumor was enlarged. Compared with that in the CT images obtained at the former hospital, the ovarian tumor was also extremely enlarged (Fig. 4b).

Dr. Shiono: We consulted a surgeon for palliative surgery, planned elective operation, excluded bevacizumab to avoid interference with postoperative wound healing, and administered FOLFIRI chemotherapy (*l*-LV 275 mg, CPT-11 220 mg, 5-FU bolus i.v. 570 mg, 5-FU c.i.v. 3500 mg) once during the preoperative waiting period.

Preoperative clinical diagnosis

1. Lynch syndrome
2. Colorectal cancer
3. Ovarian tumor, borderline tumor suspected
4. Metastatic liver tumor
5. Subileus due to mechanical obstruction by colorectal cancer

Dr. Ishioka: Please tell us the operative findings, Dr. Miura.

Dr. Miura (surgeon): First, an infant head-sized multilocular and partially villous right ovarian tumor was seen. The left ovary had shrunk. In the abdominal cavity, the disseminated lesion and a small amount of pale yellow ascites were observed at vesicouterine and Douglas pouches, which were considered to be derived from right ovarian cancer. On the other hand, there was a near circumferential 50-mm tumor in the middle portion of the descending colon. However, serous surface invasion was not recognized macroscopically. Multiple metastatic tumors were observed on the bilateral liver lobe, presenting the so-called state of "tumor liver." Because of diffuse intra-abdominal adhesions due to peritonitis carcinomatosa (PC) and definitive prognostic factors such as tumor liver or PC, we performed minimally invasive, palliative, and debulking surgery, i.e., descending colectomy, oophorectomy, and liver biopsy.

Pathological discussion

Dr. Ishioka: Dr. Watanabe, please explain the pathological findings.

Dr. Watanabe (pathologist): A circumferential type 2 tumor (30 × 25 mm) was observed in the descending colon (Fig. 5a). This loupe image illustrates the part of the tumor penetrating the serosa (Fig. 5b). Histologically, a moderately differentiated tubular adenocarcinoma (tub2)

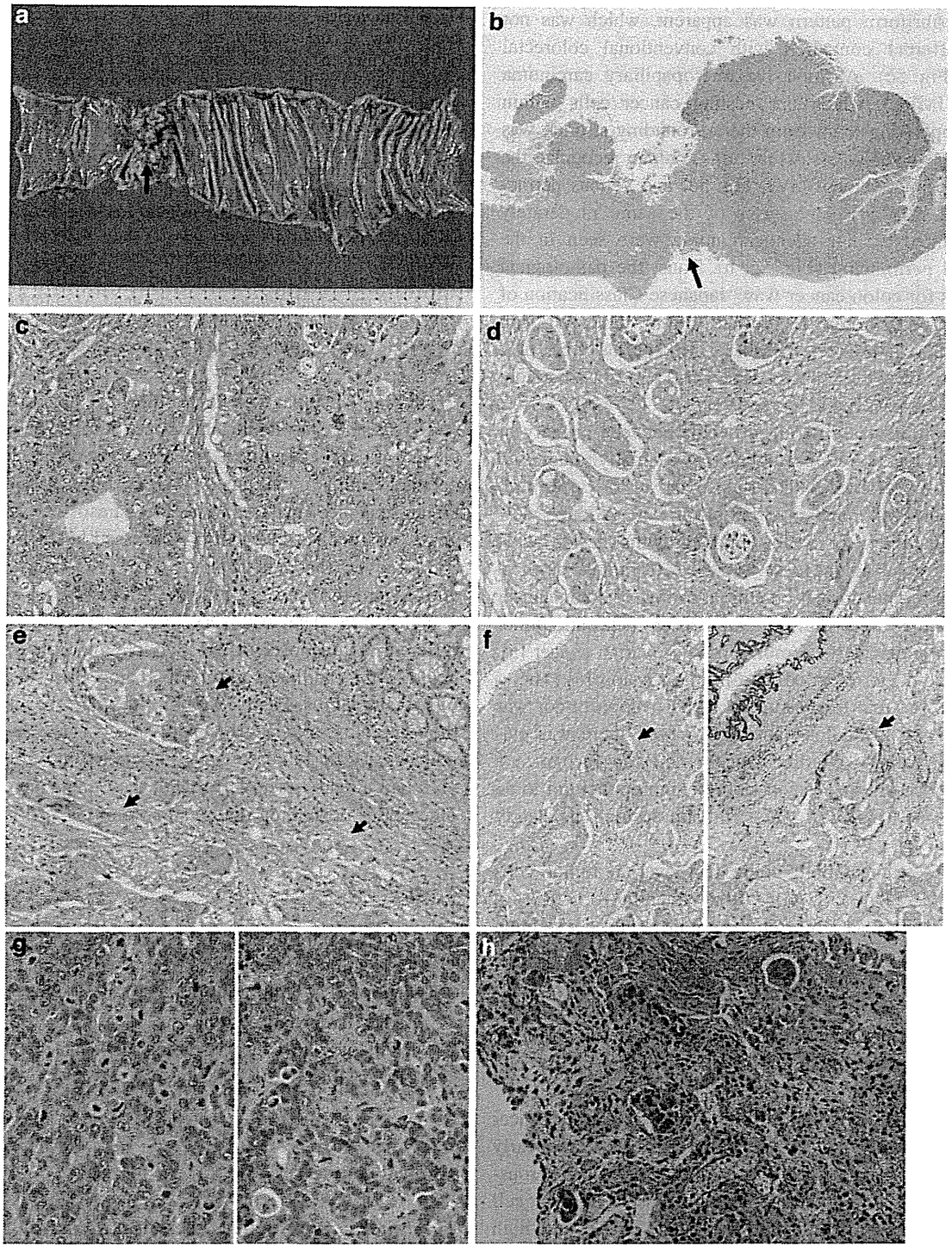


Fig. 5 Pathological findings of the descending colon cancer. **a** Macroscopic view of the resected descending colon with the cancer. A circumferential type 2 tumor (30 × 25 mm) is seen. **b** Loupe view. *Arrow* indicates the part where cancer cells penetrated the serosa. **c** Detailed microscopic view. Moderately differentiated tubular adenocarcinoma (tub2) with a cribriform pattern is apparent. There is not much difference compared with conventional colorectal cancer. **d** An invasive micropapillary carcinoma pattern (IMPC). Nesting cancer cells within spaces separating themselves from the surrounding stroma is seen in the invasive area. **e** Lymphatic involvement. *Arrows* indicate the parts. **f** Venous involvement. *Left panel* H&E stain. *Arrow* indicates the parts. *Right panel* Elastica-Masson stain for veins. *Arrow* indicates the same parts of the *left panel*. Liver (**g**) and peritoneal (**h**) metastases. The histologically similar, moderately differentiated, tubular adenocarcinomas originated from primary colon cancer are seen

with a cribriform pattern was apparent, which was not much different compared with conventional colorectal cancer (Fig. 5c). An invasive micropapillary carcinoma pattern (IMPC), which has nesting cancer cells within spaces separating them from the surrounding stroma, was seen in the invasive area (Fig. 5d). You can recognize the lymphatic involvement (1y3, Fig. 5e) and venous permeation (v2, Fig. 5f). Metastases of the same moderately differentiated tubular adenocarcinoma were seen in the liver and peritoneum (Fig. 5g, h). Thus, the pathological diagnosis for colon cancer was "Japanese Classification of Colorectal Carcinoma: D, type 2, 30 mm, tub2, pSE, int, INFb, ly3, v2, bud(−), pPM0, pDM0, pN1 (1/15), pH1 (grade A), pP1, Cy1, cM0, stage IV; TNM classification: pT4a, pN1a, pM1b, G2, stage IVB."

Although it was difficult to decide between primary or metastatic based on resemblance, we finally diagnosed primary ovarian cancer. The right ovary (180 × 150 mm) consisted of cystic and solid parts (Fig. 6a). A loupe view showed papillary or solid tumor growths beside wide necrotic lesions in the cyst (Fig. 6b). Columnar atypical cells with tubular formation similar to that of colon cancer were also observed (Fig. 6c). An ovarian metastatic tumor can morphologically resemble primary ovarian cancer [5], and the colon is regarded as a primary lesion [6]. Therefore, it is feasible to presume that the ovarian tumor was metastasis of the colon cancer. However, there was evidence of primary ovarian cancer. You can recognize a definitive transitional lesion from benign epithelium to an atypical one (Fig. 6d). This "in situ lesion" is clearly primary.

In IHC studies, both colon and ovarian tumor cells showed CA125(−), CA19-9(+), vimentin(−), CK7(−), CK20(+), CDX2(+), resembling colorectal cancer staining patterns (Fig. 6e, f). Yet, the characteristic difference between them was the staining pattern of PTEN, which supports the likelihood of ovarian serous adenocarcinoma (Table 1). Hence, the ovarian tumor was diagnosed as "serous adenocarcinoma, TNM classification: pT1c, cN0, cM0, G1, FIGO stage IC."

The features of Lynch syndrome-related ovarian cancer are as follows: young onset (mean age 48 years), early stage (FIGO stage I, 47 %), comparatively frequent serous-type histology (endometrioid 35 %, serous 28 %, clear cell 17 %, mucinous 5 %, undifferentiated 15 %), and high attribution rate of *MSH6* deficiency among underlying MMR gene mutations (*MSH2* 49 %, *MSH6* 33 %, *MLH1* 17 %) [7].

Dr. Ishioka: Please describe the MMR IHC results.

Dr. Shimodaira (medical oncologist): Whereas MLH1, MSH2, and PMS2 showed nuclear staining patterns indicating intact expression, MSH6 did not (Fig. 7). Thus, *MSH6* must be responsible gene for this case.

Fig. 6 Pathological findings of the right ovarian cancer. **a** Macroscopic view of the resected right ovary with the cancer. It is 180 × 150 mm in size and consisted of cystic and solid parts. **b** Loupe view. Papillary or solid growths of the tumor besides wide necrotic lesions are seen in the cyst. **c** Detailed microscopic view. Some columnar atypical cells with tubular formation similar to that of colon cancer were seen. **d** In situ lesion. There are epithelial cells overlaying the inner surface of the cyst, which shows definitive transitional lesions from benign epithelium to an atypical one. The in situ lesion is evidence of primary ovarian cancer. **e** IHC studies for CK7 (*left upper and right upper panels*) and CK20 (*left lower and right lower panels*). *Left upper and left lower panels* Colon cancer. *Right upper and right lower panels* Ovarian cancer. **f** IHC studies for CDX2 (*left upper and right upper panels*) and CA125 (*left lower and right lower panels*). *Left upper and left lower panels* Colon cancer. *Right upper and right lower panels* Ovarian cancer

Dr. Ishioka: What were the results of sequence analysis?

Dr. Shiono: Despite the above-mentioned IHC results of the colon cancer specimen, we could not detect any pathogenic germline mutations in *MLH1*, *MSH2*, and *MSH6* by direct sequence analyses. The mechanism of that divergence was unclear and will be discussed later.

Moreover, the genetic status of *KRAS* was wild type with regard to inspected codons 12 and 13.

Dr. Miura: That was very interesting. Concerning the differential diagnosis of the pelvic tumor, many organs could be the candidate origin, e.g., colon, bladder, prostate, ovary, and uterus. Lastly, we proposed IHC marker sets as the screening criteria [8]. Although these sets seemed unnecessary in this case because detailed molecular analyses had already been performed, they might be useful in other cases depending on the situation.

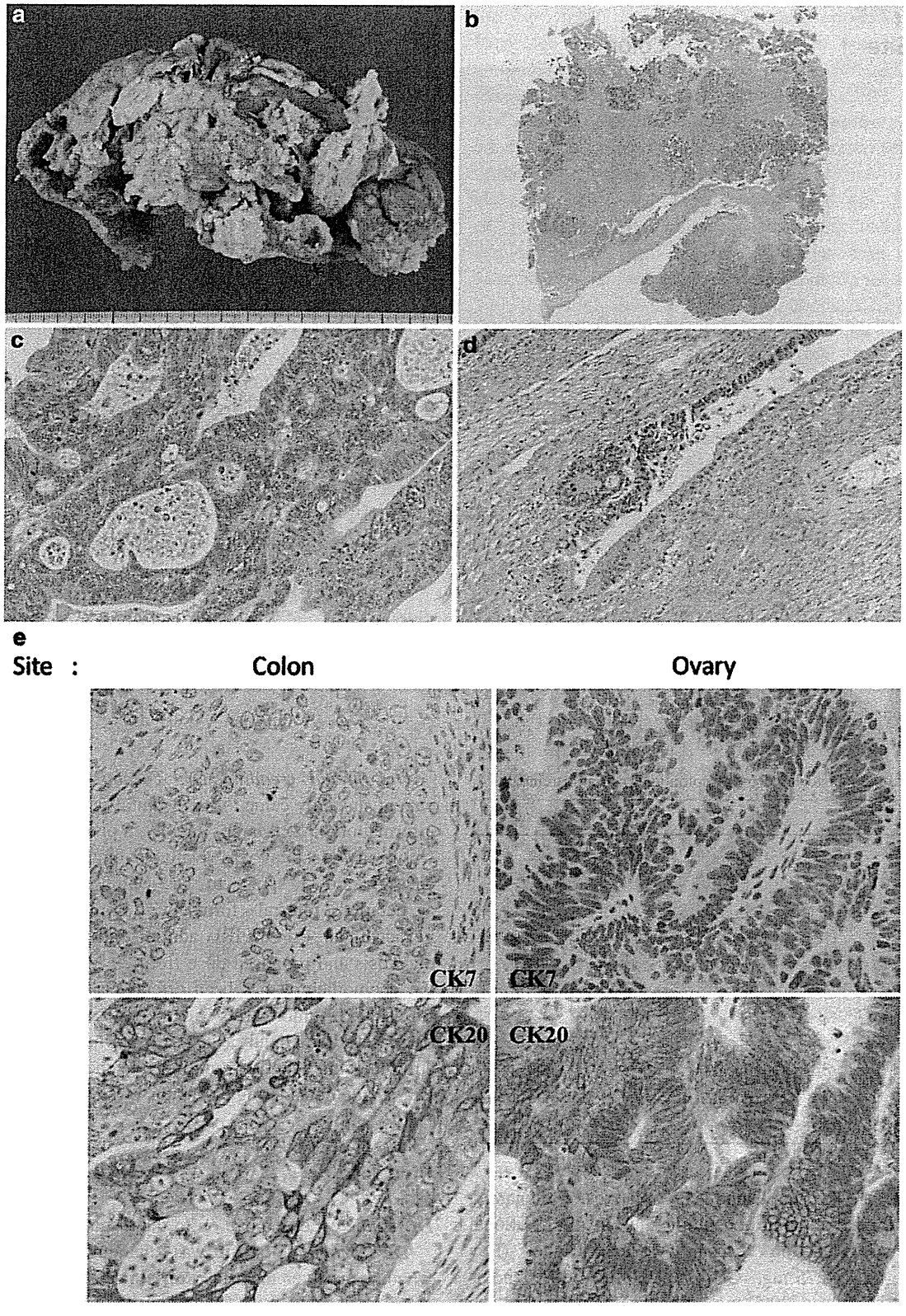
Final diagnosis

1. Lynch syndrome with MSH6 deficiency
2. Descending colon cancer (tub2, pT4a, pN1a, pM1b, stage IVB) with multiple metastases to the lymph nodes, liver, and peritoneum
3. Right ovarian cancer (serous adenocarcinoma, pT1c, cN0, cM0, G1, FIGO stage IC)

Clinical course

Dr. Ishioka: Well, tell us the clinical course after that, please.

Dr. Shiono: The postoperative course was favorable. The first visit day after discharge to restart bevacizumab + FOLFIRI therapy was 11 March 2011. While in the waiting room of the Tohoku University Hospital Cancer Center, the Great East Japan Earthquake occurred. Because she resided in the coastal area, she lost her house in the tsunami. Therefore, she moved to Fukuoka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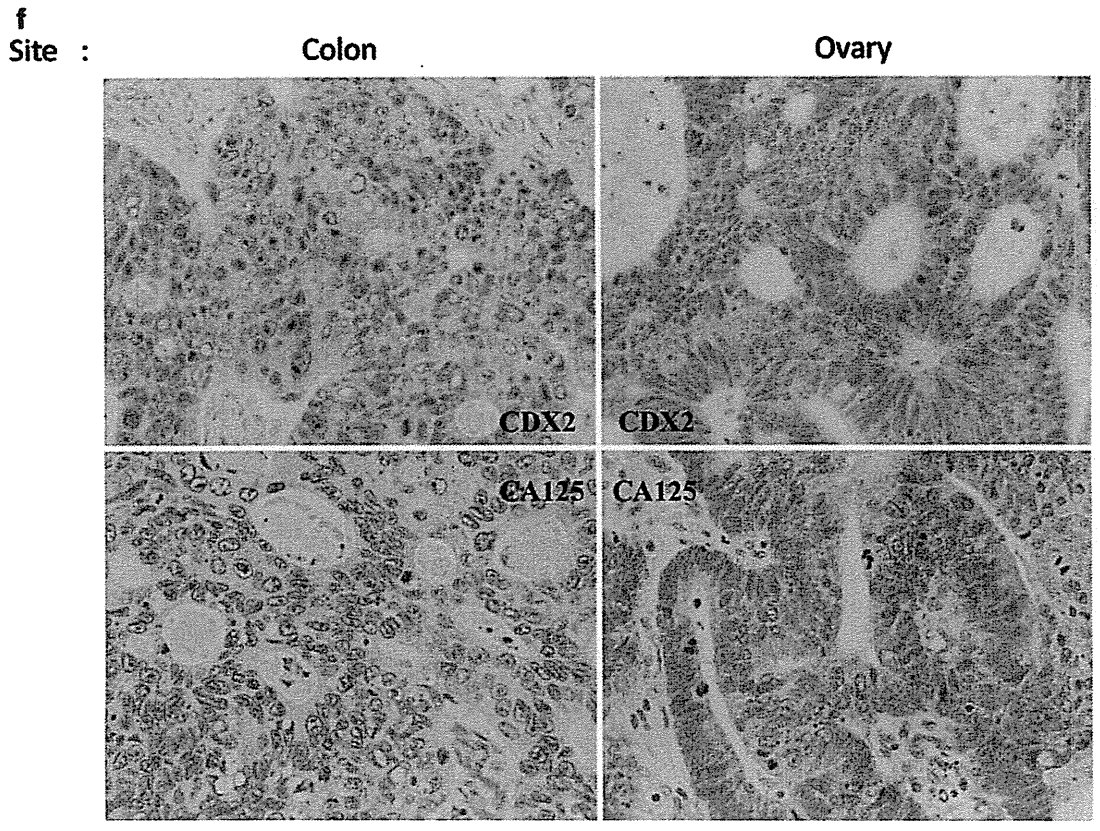

Fig. 6 continued

Table 1 Immunohistochemistry of colon and ovarian carcinomas

	Colon	Ovary
CK7	−	−
CK20	+	+
CDX2	+	+
CA125	−	−
CEA	++	++
ER	−	−
PgR	−	−
p53	+	+
p16	Focal+	Focal+
PTEN	Focal+	Diffuse++
Vimentin	−	−

prefecture on Kyushu Island with relatives. Fortunately, she restarted the same chemotherapy at the National Hospital Organization Kyushu Medical Center (Bev 230 mg, *l*-LV 275 mg, CPT-11 200 mg, 5-FU bolus 560 mg, 5-FU civ. 3000 mg). She has remained in the partial response (PR) state over a year.

Dr. Ishioka: We have a comment from Dr. Takami, who is in charge at Kyushu Medical Center. Please read it for us.

Dr. Shiono (*reading Dr. Takami's comment*): The patient suddenly came to our hospital without any medical information on 22 March. Luckily, a phone line to Tohoku University Hospital was available on that day after the disaster, and I spoke to Dr. Shiono. After receiving a detailed referral form, we immediately initiated bevacizumab + FOLFIRI administration based on the diagnosis and proposed dose from 29 March. Fortunately, the chemotherapy has been effective. The tumor marker levels and tumor sizes of the liver metastases have decreased dramatically (Fig. 8a, b). One year later, she is still receiving benefits from first-line chemotherapy, which is amazing considering her status of severe metastases.

Discussion

Dr. Ishioka: Let's move on to the discussion.

Dr. Shiono: First, it was challenging to determine whether the liver metastases originated from the colon or ovary because of the difficulty in the differential diagnosis of the pelvic tumor. In this case, the clinical response to the regimen was favorable, which was consequently in line with the histopathological assessment obtained via

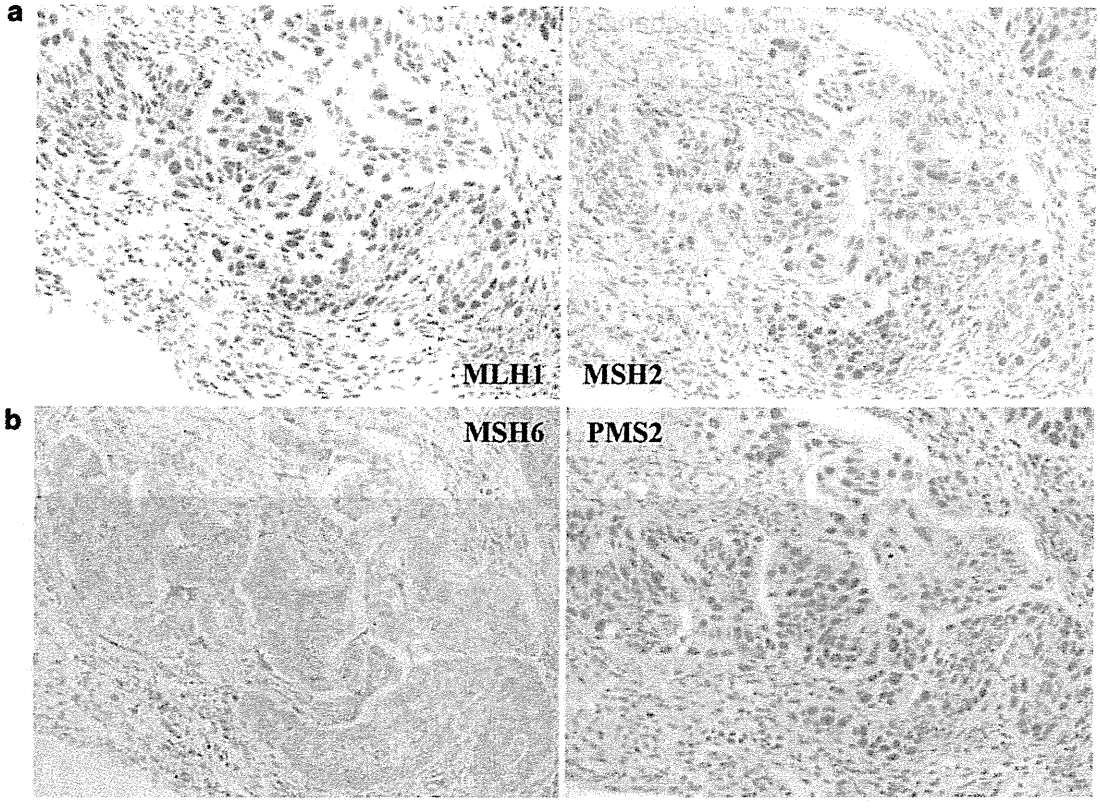

Fig. 7 IHC for MMR proteins using the colon cancer specimen. **a, b** IHC studies for MLH1 (*left upper panels*), MSH2 (*right upper panels*), MSH6 (*left lower panels*), and PMS2 (*right lower panels*). Whereas MLH1, MSH2, and PMS2 showed the nuclear staining pattern, MSH6 did not. *Left lower panel* Cytoplasmic weak and blur staining was regarded as non-specific compared to other positive and negative controls

palliative surgery. Thus, it is important to select a suitable regimen in accordance with the histology, if possible.

Dr. Ishioka: What about the practical treatment?

Dr. Shiono: In the literature, CPT-11 is clearly effective on MMR-deficient tumor cells in vitro and favorable in some clinical studies, but its clinical evidence remains controversial [9–17]. Hence, we selected the bevacizumab + FOLFIRI regimen as first-line chemotherapy for the metastatic colorectal cancer. In retrospect, because it has still been effective in the PR state for over a year, the chemotherapy choice seems to be reasonable in this case.

Dr. Ishioka: Please explain the standard first-line chemotherapy for advanced or metastatic colorectal cancer, Dr. Kakudo.

Dr. Kakudo (*medical oncologist*): There are some options. As first line chemotherapy, we choose FOLFIRI or FOLFOX (5-FU/*l*-LV/*l*-OHP) regimens as a combination of cytotoxic agents. Sequential therapy like FOLFIRI or FOLFOX regimen as first line, followed by the alternative regimen as second line, has improved outcome regardless of the order of the regimens [18]. CapeOX, the regimen using the oral prodrug of 5-FU, is another option showing an almost identical outcome compared to FOLFOX [19]. The common adverse events are different: peripheral neuropathy in *l*-OHP and diarrhea in CPT-11. The last choice is whether to add molecular-targeted agents such as bevacizumab (anti-VEGF antibody drug) or cetuximab/panitumumab (anti-EGFR antibody drugs). You should pay attention to contraindications of these monoclonal antibody drugs, e.g., the comorbid severe vascular problems in bevacizumab use. Patients with the *KRAS* gene mutation should be excluded from cetuximab/panitumumab administration. We make an optimal decision depending on the circumstances of each case [20, 21].

Dr. Shiono: In this case, CPT-11 was used as a key drug considering the Lynch syndrome background. CPT-11's effectiveness against cancer cells resulting from a MMR deficiency has been demonstrated in in vitro analyses. Although the entire mechanism remains unclear, it is speculated that CPT-11, an topoisomerase-I inhibitor, exerts its cytotoxicity by generating DNA double-strand breaks (DSBs) in the administered cell. Conversely, MMR-deficient tumor cells have a tendency to accumulate mutations within microsatellite repeats of genes associated

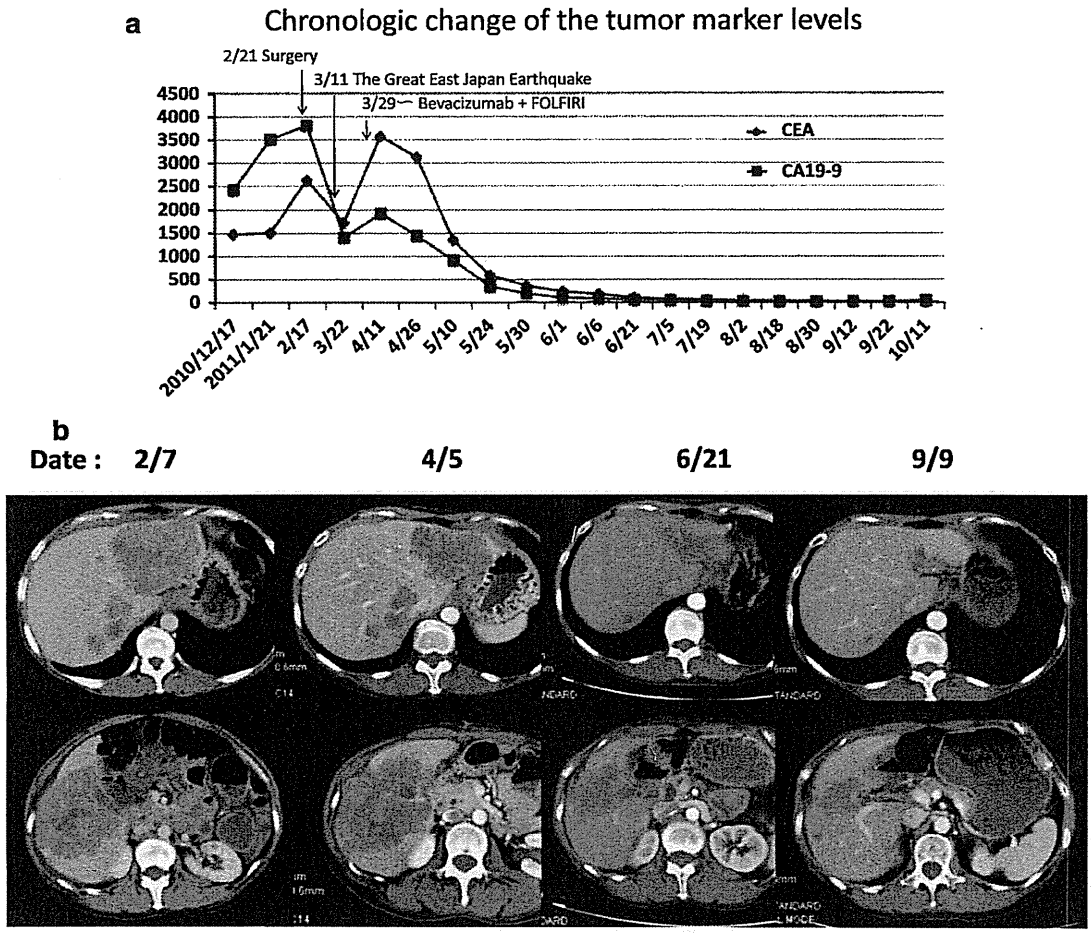

Fig. 8 Therapeutic effect of the systemic bevacizumab + FOLFIRI therapy. **a** Chronological change in the tumor marker levels. They decreased dramatically after administration of the systemic bevacizumab + FOLFIRI therapy. **b** Chronological change in liver metastases. They have decreased dramatically after administration of systemic bevacizumab + FOLFIRI therapy and have been in the PR state over a year

with DSBs repair, such as *MRE11* and *RAD50*. Taken together, MMR-deficient cells exhibit high sensitivity to CPT-11 [9–17]. Hence, CPT-11 treatment might be effective in patients with microsatellite instability-high (MSI-H) colorectal cancer.

Dr. M. Takahashi (medical oncologist): In fact, a previous randomized study for adjuvant chemotherapy against stage III MSI-H colon cancers demonstrated the significant advantage of the addition of CPT-11 [12]. However, another subsequent study did not reveal the benefit in a similar population [13]. Thus, the clinical benefit of CPT-11 compared with other agents in MSI-H colorectal cancer remains controversial. Because the mutations in *MRE11* or *RAD50* are detected in many but not all MSI-H tumors (70–85 %) [22], the MSI-H phenotype may not always correlate with the hypersensitivity of tumors to CPT-11. Another marker to indicate *MRE11* or *RAD50* deficiency (e.g., mutational analysis and/or IHC) may help to predict the efficacy of the CPT-11 treatment.

Dr. Ishioka: As both the former trials (CALGB89803 and PETACC-3) were adjuvant trials for stage II/III colorectal cancer [12, 13, 23], the clinical relevance of the outcome was slightly different in this stage IV case. While the evidence level of the advantage of CPT-11 for MSI-H tumor was not sufficient, selecting FOLFIRI among the standard therapies was reasonable according to the concept that the most promising therapy should be given priority. Moreover, when you use CPT-11, you must evaluate the patient for the *UGT1A1* gene polymorphism. Dr. Akiyama, please offer a general explanation.

Dr. Akiyama (medical oncologist): CPT-11 is inactivated by UGT1A1. If a specific gene polymorphism exists in *UGT1A1*, the glucuronidation level of SN-38, the active metabolite of CPT-11, would be attenuated, resulting in

drug accumulation and toxicity enhancement; this leads to diarrhea, neutropenia, etc. To be more precise, homozygosity for *UGT1A1*28* or *UGT1A1*6* and heterozygosity for both *UGT1A1*6* and *UGT1A1*28* are the polymorphisms mentioned in the package insert of the drug. However, optimal criteria for dosage adjustments have not been established. Moreover, there are some differences among ethnicities. In Asians, *UGT1A1*6* is more frequent than *UGT1A1*28*. Conversely, *UGT1A1*28* is much more common than *UGT1A1*6*, which is quite rare in Caucasians and African-Americans. Such discordance is derived from the different genetic background among the races [24–26].

Dr. Ishioka: With regard to dose, 150 mg/m^2 is defined as the maximal dose in Japan, although 180 mg/m^2 is the standard in Europe and the US. Accordingly, data from overseas cannot be used for direct comparisons. Many research groups, including ours, are working on this topic, and an appropriate criterion for the Japanese people needs to be established. Well, let us get back to this case. What about MSI in this case? Would you explain the reason, if you did not check?

Dr. Shiono: We obtained positive IHC results, and therefore, we did not perform an MSI examination. IHC is the best initial examination because it directs the candidate gene for subsequent mutation analysis in families with a high probability of having a mutation (the revised Bethesda guidelines or Amsterdam II criteria) [27]. Moreover, the latest analysis on the accuracy and cost-effectiveness of IHC and/or MSI examination to screen for Lynch syndrome [28] promotes the following strategies: "IHC and MSI performed simultaneously" and "IHC followed by MSI if IHCs were normal." The latter was slightly better in terms of cost. Therefore, IHC seems to be sufficient if it is performed first. According to this strategy, if IHC demonstrated the candidate mutated gene, you can skip MSI and proceed to direct sequencing. IHC has an advantage in terms of specifying the putative mutated MMR gene compared with MSI [29].

Dr. Ishioka: OK, so it is reasonable. However, how do you explain the discrepancy between the results of IHC and sequence analyses?

Dr. Shiono: As seen in Fig. 7b, nuclear staining of MSH6 alone was lost compared with that of the other three MMRs. Some possibilities were considered. For example, it is known that genomic rearrangements such as large deletions cannot be detected by conventional sequence analysis [30–32], actually in a significant proportion of Lynch syndrome families (5–20 %) [33–36]. Otherwise, it may be a type of epigenetic modification such as methylation [37]. However, further molecular analyses, e.g., the multiplex ligation-dependent probe amplification (MLPA) test, are needed for elucidation [31, 33, 38].

Dr. Ishioka: What about care for the families because this is a hereditary syndrome?

Dr. Shiono: Complying with the guidelines [39, 40], we performed a genetic counseling series for the patient, and her sister wished to accompany her. Her siblings shared the information, recognized the importance of medical follow-up, and have begun to undergo annual screening examinations, including colonoscopy. You can refer to the surveillance recommended by the international collaborative groups [27, 41]. However, a study indicated that the screening recommendations for *MSH6* mutation carriers may slightly differ from those for Lynch syndrome carriers as a whole, reflecting the characteristics of *MSH6*-mutated Lynch syndrome [42, 43]. The weaker phenotype, which is observed as a result of *MSH6* mutations, exhibits a later age of onset and lower penetrance compared with that observed as a result of *MLH1* or *MSH2* mutations [44, 45]. Many types of cancer should be considered in regard to an increased risk, e.g., cancer of the colorectum, endometrium, stomach, small intestine, hepatobiliary system, kidney, urinary bladder, brain, and ovary. The latest prospective study showed that pancreatic and breast cancers had an elevated risk [46].

Dr. Ishioka: Finally, what is the discriminative point in this case compared with other Lynch syndrome cases?

Dr. Shiono: In general, approximately 90 % of Lynch syndrome cases with mutations in any MMR genes are attributed to *MLH1* or *MSH2* mutations with distinct clinical features such as early onset (<50 years) and proximal colon predominance [47–52]. In contrast to these characteristics, it might have been difficult to diagnose Lynch syndrome in this case without a definitive family history. Moreover, with respect to comorbid cancer, while the frequency of endometrial cancer is as high as 60–70 %, the frequency of ovarian cancer is only 7–10 % [53]. Hence, clinical information on ovarian lesions might be relatively less likely to indicate Lynch syndrome. As mentioned above, although the incidence of Lynch syndrome attributed to *MSH6* mutation is as low as approximately 10 %, it is known to show "relatively late onset" and "low penetrance" propensity compared with *MLH1* or *MSH2* mutations [42, 44, 45]. Thus, judging by only clinical manifestation may lead to a diagnostic pitfall. To avoid misdiagnosis of Lynch syndrome, considering a family history is always critically important.

Dr. Shimodaira: Concerning the unique phenotype of MSH6-deficient Lynch syndrome, the mechanism can be understood when the molecular function of the four MMR proteins is considered. First, they function as heterodimers formed by MSH2 in association with MSH6 (MutSα) or MSH3 (MutSβ) and MLH1 interaction with PMS2 (MutLα), respectively. As seen in these complexes, the contribution of MSH6 is relatively small compared with that of major players such as MLH1 or MSH2, which

interact with many gene products. In fact, MSH6 functionally participates only in detection of single-base mismatch or small loop-out mutations, while MLH1 or MSH2 engages in widespread mismatches other than single-base abnormalities. Thus, the loss of MSH6 function involves only a partial deficiency of the MMR system, and subsequently it results in an attenuated clinical phenotype, which is approximated to conventional colorectal cancers with regard to late onset and low penetrance, compared with those caused by MLH1 or MSH2 deficiency [54, 55].

Dr. Shiono: In conclusion, this was a very intriguing discussion on diagnostics, treatment, pathology, and molecular biology. It is also dramatic that she was saved from the tsunami, which deprived her of her house on the seashore, by an occasional visit to our hospital during the Great East Japan Earthquake. She has also been spared from life-threatening disease progression by treatment based on the cooperation of many doctors. I appreciate all your kind collaborative work.

Dr. Ishioka: The first-line bevacizumab + FOLFIRI treatment exerted a pronounced effect on this metastatic case of *MSH6*-mutated Lynch syndrome. The population of Lynch syndrome cases with metastasis is too small to organize a large-scale randomized prospective trial in order to elucidate CPT-11 effectiveness. However, the prevalence of MSI among all colorectal cancers is approximately 15 % [56, 57]. Therefore, it might be possible to conduct a clinical trial by alternatively targeting similar types of cancers. Thus, further analysis is needed to elucidate the clinical benefit of the drug. Are there any questions? Then, this conference is adjourned. Thank you for your attendance.

What we learned from this case conference

1. You must always collect detailed information regarding family history in order not to overlook familial tumor syndromes.
2. You should know that weaker phenotypes, such as "late onset" and "low penetrance," compared to *MLH1*- or *MSH2*-mutated Lynch syndrome, can be observed because of *MSH6* deficiency.
3. A histopathological diagnosis must be obtained as soon as possible before deciding on an optimal regimen for patients with multiple primary cancers.
4. Although it is controversial at the clinical level and requires further study, a CPT-11-based regimen may have favorable effects on Lynch syndrome cases, depending on MMR deficiency.

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References

1. Vasen HF, Watson P, Mecklin JP et al (1999) New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 116:1453–1456
2. Brown DL, Zou KH, Tempany CM et al (2001) Primary versus secondary ovarian malignancy: imaging findings of adnexal masses in the Radiology Diagnostic Oncology Group Study. Radiology 219:213–218
3. Imaoka I, Wada A, Kaji Y et al (2006) Developing an MR imaging strategy for diagnosis of ovarian masses. Radiographics 26:1431–1448
4. Kim SH, Kim WH, Park KJ et al (1996) CT and MR findings of Krukenberg tumors: comparison with primary ovarian tumors. J Comput Assist Tomogr 20:393–398
5. Garcia A, De la Torre J, Castellvi J et al (2004) Ovarian metastases caused by cholangiocarcinoma: a rare Krukenberg's tumour simulating a primary neoplasm of the ovary: a two-case study. Arch Gynecol Obstet 270:281–284
6. Lash RH, Hart WR (1987) Intestinal adenocarcinomas metastatic to the ovaries. A clinicopathologic evaluation of 22 cases. Am J Surg Pathol 11:114–121
7. Ketabi Z, Bartuma K, Bernstein I et al (2011) Ovarian cancer linked to Lynch syndrome typically presents as early-onset, non-serous epithelial tumors. Gynecol Oncol 121:462–465
8. Miura K, Ishida K, Fujibuchi W et al (2012) Differentiating rectal carcinoma by an immunohistological analysis of carcinomas of pelvic organs based on the NCBI Literature Survey and the Human Protein Atlas database. Surg Today 42(6):515–525
9. Vilar E, Scaltriti M, Balmana J et al (2008) Microsatellite instability due to hMLH1 deficiency is associated with increased cytotoxicity to irinotecan in human colorectal cancer cell lines. Br J Cancer 99:1607–1612
10. Fallik D, Borrini F, Boige V et al (2003) Microsatellite instability is a predictive factor of the tumor response to irinotecan in patients with advanced colorectal cancer. Cancer Res 63:5738–5744
11. Jacob S, Aguado M, Fallik D et al (2001) The role of the DNA mismatch repair system in the cytotoxicity of the topoisomerase inhibitors camptothecin and etoposide to human colorectal cancer cells. Cancer Res 61:6555–6562
12. Bertagnolli MM, Niedzwiecki D, Compton CC et al (2009) Microsatellite instability predicts improved response to adjuvant therapy with irinotecan, fluorouracil, and leucovorin in stage III colon cancer: Cancer and Leukemia Group B Protocol 89803. J Clin Oncol 27:1814–1821
13. Tejpar S, Bosman F, Delorenzi M, Fiocca R, Yan P, Klingbiel D et al (2009) Microsatellite instability (MSI) in stage II and III colon cancer treated with 5FU-LV or 5FU-LV and irinotecan (PETACC 3-EORTC 40993-SAKK 60/00 trial). J Clin Oncol 27:(suppl; abstr 4001)
14. Bras-Goncalves RA, Rosty C, Laurent-Puig P et al (2000) Sensitivity to CPT-11 of xenografted human colorectal cancers as a function of microsatellite instability and p53 status. Br J Cancer 82:913–923
15. Giannini G, Rinaldi C, Ristori E et al (2004) Mutations of an intronic repeat induce impaired MRE11 expression in primary human cancer with microsatellite instability. Oncogene 23:2640–2647
16. Magrini R, Bhonde MR, Hanski ML et al (2002) Cellular effects of CPT-11 on colon carcinoma cells: dependence on p53 and hMLH1 status. Int J Cancer 101:23–31
17. Miquel C, Jacob S, Grandjouan S et al (2007) Frequent alteration of DNA damage signalling and repair pathways in human

colorectal cancers with microsatellite instability. Oncogene 26: 5919–5926
18. Tournigand C, Andre T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237
19. Cassidy J, Clarke S, Diaz-Rubio E et al (2008) Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 26:2006–2012
20. Chibaudel B, Tournigand C, Andre T et al (2012) Therapeutic strategy in unresectable metastatic colorectal cancer. Ther Adv Med Oncol 4:75–89
21. Kurkjian C, Kummar S (2009) Advances in the treatment of metastatic colorectal cancer. Am J Ther 16:412–420
22. Vilar E, Gruber SB (2010) Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol 7:153–162
23. Sinicrope FA, Sargent DJ (2012) Molecular pathways: microsatellite instability in colorectal cancer: prognostic, predictive, and therapeutic implications. Clin Cancer Res 18:1506–1512
24. Han JY, Lim HS, Shin ES et al (2006) Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. J Clin Oncol 24:2237–2244
25. Kaniwa N, Kurose K, Jinno H et al (2005) Racial variability in haplotype frequencies of UGT1A1 and glucuronidation activity of a novel single nucleotide polymorphism 686C>T (P229L) found in an African-American. Drug Metab Dispos 33:458–465
26. Saeki M, Saito Y, Jinno H et al (2006) Haplotype structures of the UGT1A gene complex in a Japanese population. Pharmacogenomics J 6:63–75
27. Vasen HF, Moslein G, Alonso A et al (2007) Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 44:353–362
28. Abbott DE, Cantor SB, Rodriguez-Bigas MA, Chang GJ, Lynch PM, Feig BW, Skibber JM, You YN, University of Texas M. D. Anderson Cancer Center, Houston, TX (2012) Detecting hereditary nonpolyposis colorectal cancer syndrome (HNPCC) in patients with colorectal cancer (CRC): optimal strategies at lower costs. J Clin Oncol 30:(suppl 4; abstr 396)
29. Hampel H, Frankel WL, Martin E et al (2005) Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 352:1851–1860
30. Taylor CF, Charlton RS, Burn J et al (2003) Genomic deletions in MSH2 or MLH1 are a frequent cause of hereditary non-polyposis colorectal cancer: identification of novel and recurrent deletions by MLPA. Hum Mutat 22:428–433
31. van der Klift H, Wijnen J, Wagner A et al (2005) Molecular characterization of the spectrum of genomic deletions in the mismatch repair genes MSH2, MLH1, MSH6, and PMS2 responsible for hereditary nonpolyposis colorectal cancer (HNPCC). Genes Chromosomes Cancer 44:123–138
32. Grabowski M, Mueller-Koch Y, Grasbon-Frodl E et al (2005) Deletions account for 17 % of pathogenic germline alterations in MLH1 and MSH2 in hereditary nonpolyposis colorectal cancer (HNPCC) families. Genet Test 9:138–146
33. Perez-Cabornero L, Velasco E, Infante M et al (2009) A new strategy to screen MMR genes in Lynch syndrome: HA-CAE, MLPA and RT-PCR. Eur J Cancer 45:1485–1493
34. Wang Y, Friedl W, Lamberti C et al (2003) Hereditary nonpolyposis colorectal cancer: frequent occurrence of large genomic deletions in MSH2 and MLH1 genes. Int J Cancer 103:636–641
35. Wijnen J, van der Klift H, Vasen H et al (1998) MSH2 genomic deletions are a frequent cause of HNPCC. Nat Genet 20:326–328
36. Peltomaki P (2005) Lynch syndrome genes. Fam Cancer 4:227–232
37. Moelans CB, Verschuur-Maes AH, van Diest PJ (2011) Frequent promoter hypermethylation of BRCA2, CDH13, MSH6, PAX5, PAX6 and WT1 in ductal carcinoma in situ and invasive breast cancer. J Pathol 225:222–231
38. Wang Y, Friedl W, Sengteller M et al (2002) A modified multiplex PCR assay for detection of large deletions in MSH2 and MLH1. Hum Mutat 19:279–286
39. Trepanier A, Ahrens M, McKinnon W et al (2004) Genetic cancer risk assessment and counseling: recommendations of the national society of genetic counselors. J Genet Couns 13:83–114
40. Resta R, Biesecker BB, Bennett RL et al (2006) A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns 15:77–83
41. Lindor NM, Petersen GM, Hadley DW et al (2006) Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 296:1507–1517
42. Baglietto L, Lindor NM, Dowty JG et al (2010) Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst 102:193–201
43. Hendriks YM, Wagner A, Morreau H et al (2004) Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology 127:17–25
44. Kolodner RD, Tytell JD, Schmeits JL et al (1999) Germ-line msh6 mutations in colorectal cancer families. Cancer Res 59:5068–5074
45. Wagner A, Hendriks Y, Meijers-Heijboer EJ et al (2001) Atypical HNPCC owing to MSH6 germline mutations: analysis of a large Dutch pedigree. J Med Genet 38:318–322
46. Win AK, Young JP, Lindor NM et al (2012) Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol 30:958–964
47. Box JC, Rodriguez-Bigas MA, Weber TK et al (1999) Clinical implications of multiple colorectal carcinomas in hereditary nonpolyposis colorectal carcinoma. Dis Colon Rectum 42:717–721
48. Lynch HT, Smyrk TC, Watson P et al (1993) Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. Gastroenterology 104:1535–1549
49. Mecklin JP, Jarvinen HJ (1986) Clinical features of colorectal carcinoma in cancer family syndrome. Dis Colon Rectum 29:160–164
50. Watson P, Lin KM, Rodriguez-Bigas MA et al (1998) Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. Cancer 83:259–266
51. Niessen RC, Kleibeuker JH, Westers H et al (2009) PMS2 involvement in patients suspected of Lynch syndrome. Genes Chromosomes Cancer 48:322–329
52. Peltomaki P (2003) Role of DNA mismatch repair defects in the pathogenesis of human cancer. J Clin Oncol 21:1174–1179
53. Desai TK, Barkel D (2008) Syndromic colon cancer: Lynch syndrome and familial adenomatous polyposis. Gastroenterol Clin N Am 37:47–72, vi
54. Acharya S, Wilson T, Gradia S et al (1996) hMSH2 forms specific mispair-binding complexes with hMSH3 and hMSH6. Proc Natl Acad Sci USA 93:13629–13634
55. Boland CR, Goel A (2010) Microsatellite instability in colorectal cancer. Gastroenterology 138(2073–2087):e2073
56. Poynter JN, Siegmund KD, Weisenberger DJ et al (2008) Molecular characterization of MSI-H colorectal cancer by MLHI promoter methylation, immunohistochemistry, and mismatch repair germline mutation screening. Cancer Epidemiol Biomarkers Prev 17:3208–3215
57. Samowitz WS, Curtin K, Ma KN et al (2001) Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. Cancer Epidemiol Biomarkers Prev 10:917–923