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Encephalitis as a rare complication of 5-fluorouracil

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SUMMARY
Despite constant progress in pharmacology and the introduction of subsequent, new generations of anticancer drugs into clinical use, some of the classic cytostatics still remain the basis of many oncological treatment regimens. One of such drugs is a widely used antimetabolite – 5-Fluorouracil (5-Fu). Like all drugs, it has its toxic side effects. In addition to cardiotoxicity, other systems to which 5-Fu develops toxic effects include the nervous system, the digestive system and the bone marrow.The paper presents a very rare case of drug-induced encephalitis with good long-term treatment effects, discusses drug metabolism, mechanisms of toxicity development and presents a literature review.
Keywords: rectal cancer, 5-Fluorouracil, encephalitis

I. INTRODUCTION

Colorectalcancer (of which the rectumis a part) ranks 2nd in terms of incidence in bothsexes. The majority of colorectalcarcinomasdevelop on the basis of polyps (tubularadenomas, less commonlynonpolyposis);
nonpolyposiscarcinomasdevelop on the basis of previouslyunchangedmucosa.
Amongtubularadenomas, malignantlesionsaccount for 5%; amongtubuloepitheliomas, 20%; and amongtubularadenomas, 40%. Between 15 and 35% of casesarefamilialcancers; the remainingcasesaresporadiccancers.

In order to determine the appropriatestage, testsareperformed: endoscopic (colonoscopy), imaging (CT of the thorax and abdomen, MRI of the small pelvis) and bloodtests (assessingbonemarrow, organ function and levels of tumourmarkers, especially CEA levels). MRI isused to assessboth the initiallocal status and the preoperative status. The treatment team mainlyexpectsradiologists to distinguish T2 to T4 features, assess the analsphincter and the status of the lymphnodes. Correctstagingallows for the selection of the correct management.

The treatment of rectalcancercan be eitherradicalorpalliative (in the situation of a non-resectablelesion).
Radicaltreatmentincludestwoclinicalsituations:
(1) primarysurgicaltreatment (in patients with T1-T2N0M0 stage);
(2) preoperative: chemoradiotherapy (with a dose of 50-54 Gy in fractionaldoses of 1.8-2 Gy, in combination with chemotherapyconsisting of 5-Fluorouracil with calciumfolinate and surgerydeferreduntilapproximately 6 weeksafterwards) or stand-aloneradiotherapy (administered for 5 days with a dose of 5 Gy in the weekprior to surgery) [1].

Clinicalpharmacology of 5-Fluorouracil (5-Fu)

5-Fluorouracil, a fluorinatedpyrimidine, belongs to the group of antimetabolites - pyrimidineantagonists. It retainsitsstability for many weeks in solutions at physiological pH. The drugshows a cytotoxic effect after conversion (biotransformation) to the twocorrespondingnucleotides:
fluorouridinetriphosphate (FUTP) and 5-fluoro-2`-deoxyuridine phosphate (FdUMP). The metabolism of 5-Fu followsthreepathways, by conversion to: (1) 5-fluorouridine-5`-monophosphate (FUMP) via phosphorylase and uridinekinase; (2) FUMP via orotinatephosphoribosyltransferase, and (3) FdUMP via uridinekinase and thymidinephosphorylase, the latterpathwaybeingconsidered the leastimportant. Inhibition of thymidinesynthase (TS) activityis a particularly important mechanism. The combinedadministration of 5-Fu with leucovorinenhancestreatmentefficacyprobably by stabilising the FdUMP-TS complex in the presence of the leucovorinmetabolite 5,10-methylenetetrahydrofolate, which in turnresults in a stronginhibition of DNA synthesis and consequentlyleads to celldeath. Between 5 and 20% of the drugisexcreted from the body in anunmetabolised form. The biological half-life of the drugafterrapidintravenousadministrationis 10 to 20 minutes, and the mainroute of drugexcretionis

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the gastrointestinaltract. Administration of the drug by long-term intravenousinfusionincreaseswhole-body clearance from 0.5-2 l/min (with rapidadministration) to 3-6 l/min, with the lungsratherthan the gastrointestinaltractbecoming the mainroute of excretion. Sideeffects of the druginclude, in addition to toxiceffects on the bonemarrow and intestinalepithelium, symptoms of brain and cerebellardamagefollowing high doses of the drug [2].

II. CASE REPORT

A 53-year-old femalepatient, with no significantpreviousmedicalhistory, apart from a regulatedtype II diabetesmellitus, came to ourinstitutioneightweeksaftertreatmentcarried out atanothercentre. After a stagingassessment, the patient was qualified for preoperativeradiotherapyadministering 5 Gy for 5 dayseach (25.06.-07.07.2018), followed by surgery on 16.07.2018. Microscopicexamination of the removedmaterialrevealedadenocarcinoma of intermediatemalignancy (G2), infiltration of peri-intestinaladiposetissue and involvement of 1 out of 16 lymphnodes. The tumour on macroscopicevaluation was 45 mm. The postoperativestage was set at pT3N1M0.

After a consilium, the patient was qualified for complementarychemotherapyaccording to the LF2 regimen. On 17-18.09.2018, the firstcycle was administered on anoutpatientbasis (in a rhythmevery 14 days) with good immediate tolerance. Drugdoseswerecalculated for a body surfacearea of 1.42 m2 (height - 150 cm; weight - 49 kg) according to the Nordicregimen: Leucovorin - 20 mg/m2 (= 28 mg); 5-Fluorouracil - 400 mg/m2 (= 570 mg). The drugswereabsorbedcorrectly, with no sidereactions, and the patientreported no distressingsymptomsorcomplaints. The start date for cycle 2 was set for 01.10.2018.

On 27.09.2018, the patientdevelopedanepisode of fainting with numbness of the upper limb (the informationsheet from the emergencydepartment of the hospitalshe was admitted to did not notewhich one). The followingday, seizuresoccurred, for which the patient was hospitalised from 28.09 to 04.10.2018 in anotherhospital. She was admitted to the hospital in a seriouscondition, with impairedconsciousness. In addition, bloodtestsshowed leukopenia and thrombopenia (leukocytes = 0.88x 10^3/uL; neutrophils = 0.29x 10^3/uL; platelets = 23x 10^3 /uL) - for thisreason, the patient was transfused with 4 units of KKP (plateletcellconcentrate) and givengranulocytelineagegrowthfactor (filgrastim). Afterneurologicalconsultation, a diagnosis of encephalitis was established.

An MRI of the brain and brainstemperformed on 4.10.2018 described: "multiple, diffuse, indistinctlydemarcatedareas of increasedsignal in T2-weighted images and FLAIR sequences, hypointense in T1-weighted images, located in bothcerebellarhemispheres, bothcerebellarcones, involving the cortex of bothoccipitallobes and cortical-subcorticalareas of bothfrontaland parietallobes, with zones of diffusionrestrictionperipherally in DWI images. Afterintravenousadministration of paramagneticcontrast agent, no features of contrastenhancementwerevisualisedwithinthesearea s (whichrules out meta lesions) - MRI image ambiguous - probablycorresponds to aninflammatoryprocess (ADEM?). Ventricular system symmetrical".

The suggestedpicture of ADEM (acutedisseminatedencephalomyelitis) denotesacutedisseminatedencephalomyelitis and isaninflammatorydiseasecharacterised by inflammatoryreaction and demyelination in the central nervous system, with a tendencytowardsperivascularlocalisation of the lesions. Itsoccurrenceis most oftenassociated with viralrashillnessesor past immunizations, although the causative agent of a largeproportion of casesremainsunknown [3].

Clinically, the patientdeveloped a four-limb paresis and became a recumbentpatient. Additionalexaminationsperformeddid not confirmlocalrecurrence and generalisation of the tumour.

A follow-up MRI scan of the brain on 12 November 2018 described: "in the leftcerebellarhemisphere, a 3.5 x 1.8 cm visiblefocusundergoingperipheralcontrastenhancem entafterintravenousadministration of paramagnetic. Small peripheralcontrast-enhanced foci in the leftoccipitallobe (5 mm diameter) and threefaint foci (4 mm diameter) in the posterior part of the leftparietallobe. Lesions most likely of meta nature. Hyperintense foci in T2-weighted images and FLAIR sequenceswithin the whitematter of bothcerebralhemispheres of vascularorigin. A 27 x 20 mm arachnoid cyst at the anterior pole of the lefttemporallobe. Otherwise, the cerebralstructures and the ventricular system do not show changes".

After a follow-up MRI scan of the brain on 28.11.2018, and afteranalysing the entirety of the MRI images to date, and in view of the regression of the previouslydescribedlesions and the finding of mediocre post-contrastenhancement of the lesions in the lastscan, the central nervous

system lesionswereconsidered to be inflammatory in nature.

At the time of hospitalisation in December 2018, the patient was stillrecumbent, with resolving 4 limb paresis, expressed by weakness of the leftupper limb and bothlowerlimbs, and to the leastextent of the rightupper limb.

An FDG (fluorodeoxyglucose) PET/CT scanperformed on 13.02.2020 showed no pathologicalchanges of oncologicalconcern, onlyradiotherapylesions in the sacrum.

Now, five yearsafterthisepisode, the patientis independent, with traceleft-sidedhemiparesis, stillwithoutactivecancer.

III. DISCUSSION

The drug as ananti-tumourantimetabolite was introducedintooncologytreatment in 1957 and quicklyfoundwidespreaduse in the chemotherapy of a number of cancers, whichcontinues to thisday. The range of itstoxicityincludeseffects on the gastrointestinaltract, heart, nervous system and marrow. The neurotoxicity of interest in thiscasecantakeeitheranacuteorchronic form. Severeneurologicaltoxicityafter 5-Fu therapy, maydevelop as isolatedtoxicity, i.e. also in the absence of negativeeffects on othersystems and organs. Patientsreceivinginfusions for head and neckareatumoursmainlydevelopacuteneurologicals yndromes, includingcerebellarataxia and upper motor symptoms. Neurologicaltoxicitycanalsooccur with weeklyregimens (with 24-hour infusionsbeingmoretoxicthanboluses) [4].

Twomainpatterns of encephalopathyarerecognised. The acute form isassociated with hyperammonemia and usuallyresolves with conservativetreatment. The delayed form isassociated with inflammatoryleukoencephalopathy and hasbeenreported in patientsreceiving 5-FU in combination with levamisole. Electroencephalographymayrevealdiffuseslowor thetawaves, whichissuggestive, but not characteristic, of metabolicencephalopathy. The exactaetiology of 5-FU-induced hyperammonemicencephalopathyhas not beenclearlyelucidated. Koenig and Patelpostulatedthatafter high doses of 5-FU, fluorocitrate, anintermediateproduct of 5-FU metabolism, inhibits the Krebs tricarboxylicacidcycle, which in turnimpairs the adenosinetriphosphate-dependent ureacycle, causinghyperammonemia. The osmoticeffect of accumulatedintracellularglutamine, whichis the mainmetabolicproduct of ammoniametabolism in the brain, hasbeenlinked to the pathophysiology of the increasedintracranialpressure and cerebraloedemaexhibited in manycases of hyperammonemicencephalopathy. Administration of 5-FU aloneis not considered a riskfactor for the development of hyperammonemia. Potentialaggravatingfactorsdescribed in the literatureincludeazotaemia, infections, dehydration and chronicconstipation. Hypovolaemialeads to increasedrenaltubularreabsorption of urea. Infectioncanlead to increasedtissuecatabolism and cancausedehydration with orwithoutpre-renalazotaemia. Chronicconstipationcanlead to increasedammoniaproduction in the colon through the action of bacterialurease and aminoacidoxidase [5].

5-Fu caninduceencephalopathies (Wernicke-Korsakov and hyperammonemic), whichusuallyoccurafter high cumulativedoses of the drug (of the order of 40 g), and areclinicallymanifested by alteredmental status and convulsions, with anestimatedincidence of 0.6% [6].

The differentialdiagnosisincludesstroke, non-convulsive status epilepticus, otherencephalopathies (such as uremic, hepaticordrug-induced) and infections and psychogenicdisorders. However, a history of recent 5-FU administrationiscrucial in the history. Acuteencephalopathiesareusuallyrare, reversible and do not requiretreatment, althoughdeathshavealsorarelybeenreported. In a largecase report of 21 cases of hyperammonemicencephalopathies, the mortalityrate was 17%; 57% of patientswereadmitted to the ICU and 70% made a completeneurologicalrecoverywithin 5 [2-10] days. Re-provocation with 5-FU was considered in 14 (67%) patients with neurologicalrecovery, and relapse was observed in 57% of thesepatients. No recurrence of 5-FU-induced hyperammonemicencephalopathy was observed as long as 5-FU re-administration was conducted with a reduceddose of 5-FU [7].

In contrast, cerebellardisorders and inflammatorymultifocalencephalopathy (MIL) remain, where the addition of levamisole to 5-F is a riskfactor. Thesediseaseshave no establishedcausaltreatment [8].

Multifocalinflammatoryleukoencephalopathy (MIL) is a cerebraldemyelinatingsyndromethatdevelopsafterchemotherapy with 5-fluorouracil (5-FU) and levamisole. The authorsdescribed a patientwhodeveloped MIL afteradministration of 5-FU, unrelated to levamisole. Thispatient was subsequentlydiagnosed with partialdeficiency of dihydropyrimidinedehydrogenase,

anenzymerequired for catabolism of 5-FU. The authorssuggestthat MIL is a directresult of chemotherapy with 5-FU and thatpatients with dihydropyrimidinedehydrogenasedeficiencyareatin creasedrisk of this and othertoxiceffects of 5-FU. Neurologicaltoxicityis a well-known but infrequentcomplication of 5-FU and includesperipheralneuropathy and encephalopathy. Encephalopathyafter 5-FU is less common and less welldefined, with clinicalfeaturesmoretypical of diffusemetabolicencephalopathy. It oftenoccurs with concurrentmetabolicabnormalities and cranialimagingmay be normal. MIL appears to present a distinctclinical and radiographicsyndromeresulting from the administration of 5-FU and itmay be thatpatients with DPD deficiencyhaveanincreasedrisk of this life-threateningcomplication.The toxiceffectsareprobablycaused by 5-FU itself and not by one of itsderivatives, since DPD deficiencyresults in a failure of catabolism of 5-FU. Druginteractions with levamisole and possiblyotherchemotherapeuticagentsmayplayanim portant, althoughundetermined, role in the pathogenesis of thissyndrome [9].

Encephalopathycaused by lowdoses of 5-fluorouracil is not welldocumented in the literature. Hydration and supportivetreatmentarerequired for treatment. Signs and symptoms of the diseaseresolvecompletely, with no signsorsymptomsfollowingtreatment. Neurologicaltoxicitiesmanifesting as lethargy, confusion, convulsions, cerebellarataxia and rarelyencephalopathyareknown but not verycommon. Theyareusuallycompletelyreversiblewhenthe drugisdiscontinued. Leucovorin, whichiscommonlycombined with 5-FU, enhancesantitumoureffects as well as toxicity. Fewcaseshavebeendocumented, but in most cases the neurologicalfeaturesaretransient and recoveryisoftencompletewithin a fewweeks [10].

Althoughsometheorieshavebeenproposed, the mechanisms of 5-FU neurotoxicityarepoorlyunderstood. Someresearchersbelievethat the accumulation of fluoroacetate, whichis a product of 5-FU catabolism and whichinhibits the utilisation of citratecausing a decrease in ATP production. This in turncausesinhibition of ATP-dependent carbamoylphosphatesynthetase I (CPS I) in the first step of the ureacycle, resulting in the accumulation of ammoniumions. ATP inhibits the ATP-dependent ureacycle. According to thistheory, ammonia, whichis a metabolicproduct of 5-FU, accumulates in largequantitiesafter a high dose of 5-FU. Therefore, encephalopathyoccurslater, accompanied by hyperammonemia and lactateacidosis. Anothertheory to explain the neurologicaladverseeffects of 5-FU therapyisthat the drugcausesthiaminedeficiency. The active form of the vitaministhiaminepyrophosphate (TPP). Exposure to 5-FU mayincrease TPP levels. Thistheoryissupported by the factthat the symptoms of Wernicke-Korsakovsyndrome, includingataxia, nystagmus, confusion and cognitivechanges, aresimilar to the neurotoxiceffects of fluorouracil. Dehydropyrimidinedehydrogenase (DPD) is the enzymethatdegrades 5-FU, and DPD isdistributed in the liver, gastrointestinalmucosa and peripherallymphocytes. Morethan 80% of administered 5-FU iscatabolised by DPD.Thus, deficiency of thisenzymecancause life-threateningorfataltoxicitywhen the patientistreated with fluoropurimidine-basedchemotherapy. The prevalence of DPD deficiency in cancerpatientsisestimated to be 2.7 per cent, and thisdiseasecan be accompanied by severefluorouraciltoxicity [11].

Inhibition of ATP productionisalsothought to be the cause of lactateacidosis, oftenobserved in cases of 5-fluorouracil toxicity [12].

5-FU-induced encephalopathyoccurs in 5.7% of patientstreated with high-dose 5-FU chemotherapy. Twodifferentdisturbedmetabolicpathwaysareknown to contribute to the development of 5-FU-induced encephalopathy. The firstisdihydropyrimidinedehydrogenase (DPD) deficiency. DPD is the mainenzymethatinactivates 5-FU, and patients with DPD deficiencymayexperiencesymptomsassociated with 5-FU accumulation. DPD deficiencyisfound in 2.7 per cent of cancerpatients and isthought to be due to mutations in the DPD gene, whichencodes DPD enzymes. With DPD deficiency, high concentrations of 5-FU penetrate the cerebrospinal fluid and causeacutedemyelination of neuronsthere. The secondis the catabolictype of 5-FU, whichisknown to be a mildertypethan DPD deficiency. According to thismechanism, the maincatabolicpathwaysremainintact and transientaccumulation of catabolite 5-FU causesencephalopathy by high 5-FU infusionrates. Koenig et al. explainedthat the administration of high doses of 5-FU inducesfluoroacetateaccumulation and directlyinhibits the Krebs cycle. Consequently, transienthyperammonemiadevelopsdue to impairment of the ATP-dependent ureacycle. Renaldysfunction and dehydration, constipation and weightlosscan be cited as factorsexacerbating

5-FU-induced encephalopathy. In patients with renaldysfunctionorpatients in dehydration, bloodlevels of a 5-FU catabolitesuch as fluoroacetateorammoniawillincrease, causingencephalopathy [13].

IV. CONCLUSIONS

- - 5-FU-associated encephalopathyhas the followingclinicalcriteria for itsdiagnosis: (1) the development of encephalopathyoccursduringorshortlyafter the end of 5-FU administration; (2) othermetabolicfactorsthatmayaffectconsciousness and mentalfunctioning, such as hypoglycaemia, organ failure, electrolyteimbalance, sepsis and central nervous system involvement by a neoplasm, should be excluded; and (3) no adverseeffectsareobservedthatmayhavebeeninduced by concomitantadministration of otherdrugs.
- - The scope of additionalbloodtests, following the neurological and psychiatricexamination of a patientreceiving 5-fluorourail, shouldincludeanassessment of serum ammonialevels.
- - The recommendedtreatmentis to discontinuechemotherapy as soon as possible, followed by hydration of the patient and administration of lactulose.
- - Properidentification and rapiddiagnosis of 5-fluorouracil-related hyperammonemicencephalopathyisessential, as recovery from treatmentisrapid [12].
- - For the treatment of severeforms, uridinetriacetate, the antidote of 5-FU, isused.
- - Allphysicians, especiallyemergencyphysicians, generalpractitioners and oncologists, should be aware of the possibility of theseraresideeffects of 5-FU chemotherapy and should be familiar with methods of diagnosing and treatingit.

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