

Lek. Siavash Świeczkowski-Feiz

Chirurgiczne postępowanie w krwawieniach do nadnerczy

Surgical Management of Adrenal Hemorrhage

Promotor: dr hab. n. med. Sadegh Toutounchi

Promotor pomocniczy: dr n. med. Wawrzyniec Jakuczun

Klinika Chirurgii Ogólnej, Naczyniowej, Endokrynologicznej i Transplantacyjnej
Uniwersyteckiego Centrum Klinicznego Warszawskiego Uniwersytetu Medycznego



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Adrenalectomia klasyczna (otwarta)

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Open adrenalectomy

Podziękowania

Pragnę złożyć najserdeczniejsze podziękowania i wyrazy wdzięczności:

Panu dr. hab. n. med. Sadeghowi Toutounchi,
promotorowi mojej pracy doktorskiej,
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Artykuły			
1.	Świeczkowski-Feiz S., Kaszczewski P., Gelo R., Krajewska E., Celejewski K., Toutounchi S., Ambroziak U., Pogorzelski R., Gałązka Z. Huge Hematoma as the First Manifestation of Adrenocortical Carcinoma: A Case Report. American Journal of Case Reports, 2023; 24: e937569. DOI: 10.12659/AJCR.937569	1	70
2.	Świeczkowski-Feiz S., Toutounchi S., Kaszczewski P., Krajewska E., Celejewski K., Gelo R., Pogorzelski R., Gałązka Z. Characteristics of Adrenal Hemorrhage: A Single Clinic's Experience. Polski Przegląd Chirurgiczny, 2024; 96(4): 36-43. DOI: 10.5604/01.3001.0054.45	0,7	100
3.	Świeczkowski-Feiz S., Toutounchi S., Krajewska E., Celejewski K., Gelo R., Kaszczewski P., Jakuczun W., Ambroziak U., Gałązka Z. Adrenal Hemorrhage: Diagnostics, Management, and Treatment. Review and Clinical Update. Videosurgery and Other Miniinvasive Techniques, 2025; 20(3): 255-260. DOI: 10.20452/wiitm.2025.17981	1.9	70
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Wykaz skrótów

ACC – adrenocortical carcinoma

AH – adrenal hemorrhage

CT – computed tomography

ESE – European Society of Endocrinology

HU – Hounsfield units

MRI – magnetic resonance imaging

SD – standard deviation

US – ultrasonography

ESES – European Society of Endocrine Surgeons

ENSAT – European Network for the Study of Adrenal Tumours

Streszczenie

Krwotok nadnerczowy, krwawienie do nadnercza (AH) jest rzadkim, a jednocześnie potencjalnie zagrażającym życiu stanem, który może być atraumatyczny lub może być następstwem urazu. Obraz kliniczny jest niespecyficzny – najczęściej obejmuje bóle w okolicy lędźwiowej lub jamy brzusznej, bóle lewej lub prawej flanki jamy brzusznej, nudności, osłabienie, hipotonię, a w przypadkach obustronnych może prowadzić do niewydolności nadnerczy.

Rozpoznanie AH często jest przypadkowe i nie jest pierwszą podejrzaną przyczyną bólów brzucha lub hipotonii u chorych zgłaszających się do Szpitalnych Izb Przyjęć czy Szpitalnych Oddziałów Ratunkowych. Mimo licznych prac naukowych wciąż brakuje jednoznacznych wytycznych dotyczących postępowania terapeutycznego.

Cykl trzech publikacji składających się na niniejszą rozprawę doktorską obejmuje:

- opis przypadku, w którym krwotok był pierwszym i jedynym objawem raka kory nadnercza,
- analizę retrospektywną dużej grupy pacjentów z krwawieniem do nadnerczy,
- oraz przegląd systematyczny literatury poświęcony tej patologii.

Celem całego cyklu była dokładna analiza przypadków oraz pogłębienie wiedzy na temat etiologii, diagnostyki i leczenia krwotoku nadnerczowego; jednocześnie stanowi on propozycję praktycznego schematu postępowania.

Publikacja 1.

Świeczkowski-Feiz S., Kaszczewski P., Gelo R., Krajewska E., Celejewski K., Toutounchi S., Ambroziak U., Pogorzelski R., Gałązka Z. *Huge Hematoma as the First Manifestation of Adrenocortical Carcinoma: A Case Report. American Journal of Case Reports*, 2023; 24: e937569. DOI: 10.12659/AJCR.937569.

Praca opisuje przypadek 38-letniego pacjenta, u którego masywny krwotok do guza nadnercza był pierwszym i jedynym objawem raka kory nadnercza. Po wstępnym leczeniu zachowawczym i stabilizacji stanu chorego zakwalifikowano go do przyspieszonej prawostronnej adrenalektomii. Po przygotowaniu farmakologicznym oraz pełnej diagnostyce hormonalnej chorego operowano w sposób klasyczny z powodu pęknięcia torebki nadnercza. Wynik histopatologiczny – rak kory nadnerczy. W tej pracy zwracamy uwagę na brak jednoznacznych algorytmów postępowania oraz konieczność bazowania na doświadczeniu ośrodka klinicznego. Zwracamy też uwagę na to, jak zdradliwe może

być krwawienie do nadnerczy bez klinicznych oraz biochemicznych cech raka kory nadnerczy i że wymaga ono zachowania ostrożności i czujności onkologicznej.

Publikacja 2.

Świeczkowski-Feiz S., Toutouchi S., Kaszczewski P., Krajewska E., Celejewski K., Gelo R., Pogorzelski R., Gałązka Z. *Characteristics of Adrenal Hemorrhage: A Single Clinic's Experience.* **Polski Przegląd Chirurgiczny**, 2024; 96(4): 36-43. DOI: 10.5604/01.3001.0054.4570

W tej pracy poddaliśmy analizie wszystkich chorych, u których stwierdzono krwawienie do nadnercza w badaniu histopatologicznym. Spośród 645 adrenalektomii, aż 199 wykazywało histopatologiczne cechy krwawień do nadnerczy, przy czym 39 chorych miało postawione rozpoznanie jeszcze przed operacją. W tej pracy pokazujemy, że w sytuacji kiedy mamy do czynienia z rozpoznaniem AH przed operacją, najczęstszą przyczyną jest pheochromocytoma (28%; n = 11), rak kory nadnerczy (10,26%; n = 4) oraz gruczolaki kory nadnerczy (23,07%; n = 9). W AH rozpoznanym pooperacyjnie rozkład jest zbliżony: pheochromocytoma (n = 54), adrenal adenoma (n = 68) i rak kory nadnerczy (n = 17).

Praca wykazuje, że aż 46% krwawień do nadnerczy rozpoznanych przed operacją jest spowodowanych guzem chromochłonnym, gruczolakiem nadnerczy, rakiem kory nadnerczy i przerzutami. Udowadniamy, że bardzo istotna jest wczesna kwalifikacja oraz przygotowanie do leczenia operacyjnego.

Publikacja 3.

Świeczkowski-Feiz S., Toutouchi S., Krajewska E., Celejewski K., Gelo R., Kaszczewski P., Jakuczun W., Ambroziak U., Gałązka Z. *Adrenal Hemorrhage: Diagnostics, Management, and Treatment. Review and Clinical Update. Videosurgery and Other Miniinvasive Techniques*, 2025; 20(3): 255-260. DOI: 10.20452/wiitm.2025.17981.

Przegląd obejmujący 41 publikacji przedstawia aktualny stan wiedzy dotyczący etiologii, diagnostyki i leczenia AH. Autorzy omówili urazowe i nieurazowe przyczyny krwotoku, charakterystyczne cechy obrazowe w USG, TK i MRI, zasady diagnostyki hormonalnej oraz wskazania do leczenia chirurgicznego.

Na podstawie danych własnych i literaturowych zaproponowano algorytm postępowania klinicznego:

- w przypadkach niestabilnych hemodynamicznie lub przy przerwaniu torebki zalecamy operację otwartą,
- w przypadkach stabilnych z krwotokiem ograniczonym do torebki – adrenalektomia laparoskopowa, nawet w guzach o średnicy większej niż 6 cm, pod warunkiem dużego doświadczenia zespołu operacyjnego.

Abstract

Adrenal hemorrhage (AH) is a rare but potentially life-threatening condition that may occur atraumatically or as a consequence of trauma. Its clinical presentation is nonspecific—most commonly including lumbar or abdominal pain, flank pain, nausea, weakness, hypotension, and, in bilateral cases, adrenal insufficiency.

The diagnosis of AH is often incidental and is not usually the first suspected cause of abdominal pain or hypotension in patients presenting to Emergency Departments. Despite numerous publications, clear therapeutic guidelines are still lacking.

This doctoral dissertation consists of three complementary papers, which include:

- a case report in which adrenal hemorrhage was the first and only manifestation of adrenocortical carcinoma,
- a retrospective analysis of a large cohort of patients with adrenal hemorrhage,
- and a systematic review of the literature on this pathology.

The aim of the entire cycle was to thoroughly analyze clinical cases and expand knowledge on the etiology, diagnosis, and management of adrenal hemorrhage, while also proposing a practical clinical management algorithm.

Publication 1.

Świeczkowski-Feiz S., Kaszczewski P., Gelo R., Krajewska E., Celejewski K., Toutounchi S., Ambroziak U., Pogorzelski R., Gałązka Z. *Huge Hematoma as the First Manifestation of Adrenocortical Carcinoma: A Case Report.* **American Journal of Case Reports**, 2023; 24: e937569. DOI: 10.12659/AJCR.937569.

This paper describes a case of a 38-year-old patient in whom a massive hemorrhage into an adrenal tumor was the first and only manifestation of adrenocortical carcinoma. After initial conservative management and stabilization, he was qualified for expedited right adrenalectomy. Following pharmacologic preparation and full hormonal evaluation, the patient underwent open surgery due to capsule rupture. Histopathology confirmed adrenocortical carcinoma.

The case highlights the absence of clear management algorithms and the necessity of relying on the experience of the clinical center. It also underscores how deceptive adrenal hemorrhage may be in the absence of clinical or biochemical features of adrenocortical carcinoma, requiring oncologic vigilance.

Publication 2.

Świczkowski-Feiz S., Toutounchi S., Kaszczewski P., Krajewska E., Celejewski K., Gelo R., Pogorzelski R., Gałazka Z. *Characteristics of Adrenal Hemorrhage: A Single Clinic's Experience.* **Polski Przegląd Chirurgiczny**, 2024; 96(4): 36–43. DOI: 10.5604/01.3001.0054.4570.

In this study, we analyzed all patients in whom adrenal hemorrhage was confirmed histopathologically. Among 645 adrenalectomies, 199 showed histopathological features of adrenal hemorrhage, of which 39 were diagnosed preoperatively. We demonstrated that, when AH is diagnosed before surgery, the most common causes include pheochromocytoma (28%,; n = 11), adrenocortical carcinoma (10,26%; n = 4), and adrenal adenomas (23,07%; n = 9). In cases diagnosed postoperatively, the distribution was similar: pheochromocytoma (n = 54), adrenal adenoma (n = 68) and adrenocortical carcinoma (n = 17).

The study shows that 46% of adrenal hemorrhages diagnosed preoperatively are caused by pheochromocytoma, adrenal adenoma, adrenocortical carcinoma, or metastases. We demonstrate the importance of early qualification and adequate preparation for surgical treatment.

Publication 3.

Świczkowski-Feiz S., Toutounchi S., Krajewska E., Celejewski K., Gelo R., Kaszczewski P., Jakuczun W., Ambroziak U., Gałazka Z. *Adrenal Hemorrhage: Diagnostics, Management, and Treatment. Review and Clinical Update. Videosurgery and Other Miniinvasive Techniques*, 2025; 20(3): 255–260. DOI: 10.20452/wiitm.2025.17981.

This review of 41 publications summarizes the current state of knowledge regarding the etiology, diagnosis, and treatment of AH. The authors discuss traumatic and non-traumatic causes of hemorrhage, characteristic imaging features in ultrasound, CT, and MRI, principles of hormonal evaluation, and indications for surgical intervention.

Based on both the authors' data and the literature, a clinical management algorithm is proposed:

- in hemodynamically unstable patients or in cases of capsule rupture — open adrenalectomy,
- in stable patients with hemorrhage confined to the adrenal capsule — laparoscopic adrenalectomy, even for tumors larger than 6 cm, provided that the surgical team has extensive experience.

Wstęp

Krwawienia do nadnerczy są rzadkim, ale potencjalnie śmiertelnym stanem klinicznym, który może mieć zarówno charakter pourazowy, jak i atraumatyczny. Obraz kliniczny jest niespecyficzny — najczęściej obejmuje nagły ból w okolicy lędźwiowej lub brzucha, nudności, wymioty, hipotonię, osłabienie, a w przypadkach obustronnych może dojść do ostrej niewydolności nadnerczy, stanowiącej zagrożenie życia. Etiologia AH jest zróżnicowana i obejmuje urazy, zaburzenia krzepnięcia, leczenie przeciwzakrzepowe, infekcje septyczne, stres operacyjny, a także zmiany nowotworowe, takie jak guz chromochłonny czy rak kory nadnerczy.

Diagnostyka opiera się głównie na badaniach obrazowych — tomografii komputerowej i rezonansie magnetycznym — oraz ocenie profilu hormonalnego. Leczenie zależy od stanu hemodynamicznego chorego i rozległości krwawienia: w przypadkach chorych stabilnych możliwe jest postępowanie zachowawcze lub laparoskopowa adrenalektomia, natomiast w sytuacjach zagrażających życiu konieczna bywa pilna adrenalektomia klasyczna.

Mimo licznych opisów pojedynczych przypadków istnieje niewielka liczba badań retrospektywnych, w których brak jest precyzyjnych sformułowań oraz przedstawienia jasnego postępowania. Z uwagi na rzadkość występowania choroby każda praca dotycząca tej tematyki stanowi istotne ugruntowanie i uzupełnienie dotychczasowej wiedzy. Publikacje stanowiące cykl prezentowanej rozprawy doktorskiej systematyzują dotychczasową wiedzę, a także pokazują gotową ścieżkę diagnostyczną i terapeutyczną oraz nakazują wysoką czujność onkologiczną.

W niniejszym cyklu prac szczególną uwagę poświęcono krwawieniom do nadnerczy rozpoznanym przed operacją, u chorych trafiających do Szpitalnych Izb Przyjęć lub Szpitalnych Oddziałów Ratunkowych, które były pierwszym objawem choroby nadnerczy. Nie należy jednak bagatelizować grupy chorych z rozpoznaniem już guza nadnerczy, którzy oczekują na operację i zgłaszają bóle w okolicy lędźwiowej, które są przypisywane bólom pochodzącym od kręgosłupa.

Pierwszą publikację cyklu rozprawy doktorskiej (Świeczkowski-Feiz S., Toutounchi S., Kaszczewski P., Krajewska E., Celejewski K., Gelo R., Pogorzelski R., Gałązka Z. *Huge Hematoma as the First Manifestation of Adrenocortical Carcinoma – A Case Report*. American Journal of Case Reports. 2023; 24: e937569) stanowi opis przypadku wraz z przeglądem literatury. Artykuł przedstawia 38-letniego pacjenta, u którego masywny krwotok do przestrzeni zaotrzewnowej był pierwszym objawem raka kory nadnercza (adrenocortical carcinoma, ACC). W wykonanym badaniu tomografii komputerowej jamy brzusznej uwidoczniono dużą, niejednorodną masę nadnerczową z rozległym

krwiakiem sięgającym lewej przestrzeni zaotrzewnowej. Wyniki badań hormonalnych nie wykazały nadczynności guza, jednak ze względu na możliwość utajonego pheochromocytoma pacjent został przygotowany farmakologicznie do zabiegu z zastosowaniem blokerów α -adrenergicznych. Zabieg adrenalektomii przeprowadzono w trybie planowym przyspieszonym, a analiza histopatologiczna wykazała raka kory nadnercza o niskim indeksie proliferacyjnym (Ki-67 <5%) z ogniskami wylewów krwi i martwicy. Obraz kliniczny oraz histopatologiczny potwierdził, że krwotok do nadnercza może stanowić pierwszy objaw nowotworu złośliwego nadnercza, nawet w przypadku braku charakterystycznych cech w badaniach obrazowych i laboratoryjnych.

Autorzy podkreślili konieczność zachowania czujności onkologicznej u pacjentów z guzem nadnercza i krwawieniem o niejasnej etiologii, a także znaczenie odpowiedniego przygotowania przedoperacyjnego w kierunku potencjalnie czynnych hormonalnie zmian. Publikacja zwraca uwagę, że właściwa ocena kliniczna, diagnostyka obrazowa i endokrynologiczna oraz planowa interwencja chirurgiczna pozwalają uniknąć opóźnień diagnostycznych i poprawić wyniki leczenia w przypadkach guzów nadnerczy o nietypowej prezentacji.

Drugą publikację cyklu rozprawy doktorskiej (Świeczkowski-Feiz S., Toutounchi S., Kaszczewski P., Krajewska E., Celejewski K., Gelo R., Pogorzelski R., Gałązka Z. *Characteristic of Adrenal Hemorrhage: A Single Clinic's Experience*. Polski Przegląd Chirurgiczny. 2024; 96(4): 36–43.) stanowi retrospektywna analiza kliniczno-patomorfologiczna pacjentów po adrenalektomii, u których w badaniu histopatologicznym stwierdzono obecność krwotoku nadnerczowego. Badaniem objęto 199 pacjentów operowanych w jednym ośrodku chirurgii endokrynologicznej w latach 2012–2022. U wszystkich chorych potwierdzono histopatologicznie obecność wylewów krwi w obrębie nadnercza, jednak rozpoznanie krwotoku przedoperacyjnie postawiono jedynie u 39 pacjentów (19,6%), natomiast u pozostałych 160 chorych (80,4%) AH rozpoznano dopiero po zabiegu, na podstawie badania histopatologicznego. W grupie z rozpoznaniem przedoperacyjnym zmiany charakteryzowały się większymi rozmiarami (średnio ponad 70 mm), niejednorodną strukturą w badaniach obrazowych oraz obecnością objawów bólowych lub epizodów hemodynamicznych. Pacjenci ci byli kwalifikowani do planowych operacji po krótkim przygotowaniu z zastosowaniem blokerów α -adrenergicznych, a decyzję o wyborze dostępu chirurgicznego podejmowano indywidualnie w zależności od stanu ogólnego i charakteru zmiany.

W grupie z rozpoznaniem pooperacyjnym dominowały przypadki o przebiegu skąpoobjawowym lub bezobjawowym, w których krwotok stanowił przypadkowe znalezisko w badaniu histopatologicznym. Najczęstszymi przyczynami AH w całej analizowanej grupie były: pheochromocytoma (28%), gruczolaki kory nadnercza (34%) oraz raki kory nadnercza (8%). Dobór techniki operacyjnej uzależniono od stanu hemodynamicznego chorego oraz integralności torebki nadnercza. U pacjentów stabilnych, z krwotokiem ograniczonym do torebki, laparoskopowa

adrenalektomia była metodą z wyboru i cechowała się wysokim profilem bezpieczeństwa. W przypadkach z pęknięciem torebki, rozległym krwotokiem lub podejrzeniem złośliwości zastosowano klasyczny dostęp otwarty, umożliwiający pełną kontrolę pola operacyjnego. W pracy podkreśliliśmy znaczenie pełnego przygotowania przedoperacyjnego, w tym rutynowego stosowania α -blokady w przypadkach, w których nie można jednoznacznie wykluczyć guza chromochłonnego. Wczesna, planowa adrenalektomia po krótkim przygotowaniu farmakologicznym pozwalała na uzyskanie dobrych wyników leczenia i zmniejszenie ryzyka powikłań hemodynamicznych.

Praca stanowi istotny wkład w poznanie klinicznego znaczenia krwotoku nadnerczowego, wykazując, że AH jest objawem wtórnym patologii guza, a jego rozpoznanie i sposób leczenia zależą od doświadczenia klinicznego oraz właściwej interpretacji badań obrazowych i hormonalnych. Uzyskane wyniki dostarczają praktycznych wskazówek dotyczących diagnostyki, kwalifikacji do leczenia operacyjnego oraz doboru techniki chirurgicznej u pacjentów z guzami nadnerczy z komponentą krwotoczną.

Trzecią publikację cyklu rozprawy doktorskiej (*Świeczkowski-Feiz S., Toutounchi S., Kaszczewski P., Krajewska E., Celejewski K., Gelo R., Pogorzelski R., Gałązka Z. Adrenal Hemorrhage: Diagnostics, Management, and Treatment. Review and Clinical Update. Videosurgery and Other Miniinvasive Techniques. 2025; 20(3): 255–260*) stanowi przegląd piśmiennictwa dotyczący diagnostyki i leczenia krwotoku nadnerczowego, opracowany na podstawie analizy 41 publikacji naukowych. Celem pracy było usystematyzowanie aktualnej wiedzy na temat etiologii, diagnostyki obrazowej i endokrynologicznej oraz strategii terapeutycznych w AH, a także opracowanie praktycznego algorytmu postępowania klinicznego. Autorzy dokonali przeglądu przypadków obejmujących zarówno krwotoki pourazowe, jak i samoistne, ze szczególnym uwzględnieniem krwotoków związanych z obecnością guzów nadnerczy. W pracy przedstawiono algorytm postępowania, w którym kluczowe znaczenie ma ocena stanu hemodynamicznego pacjenta oraz ciągłości torebki nadnercza. W przypadkach niestabilnych hemodynamicznie lub z pęknięciem torebki guza rekomendowanym sposobem leczenia jest adrenalektomia otwarta, umożliwiającą lepszą kontrolę pola operacyjnego.

W przypadkach stabilnych klinicznie, z krwotokiem ograniczonym do torebki, laparoscopia stanowi metodę z wyboru, również przy guzach większych niż 6-8 cm, jeśli doświadczenie ośrodka na to pozwala.

Zwracamy szczególną uwagę na konieczność pełnej diagnostyki endokrynologicznej przed zabiegiem, w tym oznaczenia metoksykatecholamin, kortyzolu i aldosteronu, oraz rutynowego stosowania α -blokady, gdy nie można wykluczyć guza chromochłonnego. Podkreślono również potrzebę ścisłej

współpracy zespołów chirurgicznych i endokrynologicznych w celu optymalizacji procesu diagnostyczno-terapeutycznego.

Przegląd ten stanowi podsumowanie dotychczasowych doświadczeń i jednocześnie propozycję standaryzacji postępowania w krwotoku nadnerczowym. Zaproponowany algorytm ma znaczenie praktyczne, porządkuje zasady kwalifikacji chorych do leczenia operacyjnego oraz może stanowić punkt wyjścia do dalszych badań prospektywnych i opracowania wytycznych postępowania klinicznego.

Założenia i cel cyklu publikacji stanowiących rozprawę doktorską

1. Analiza kliniczna i patomorfologiczna krwotoku nadnerczowego na podstawie własnych materiałów obejmujących pacjentów zakwalifikowanych do adrenalektomii z rozpoznaniem przed- i pooperacyjnym AH, ze szczególnym uwzględnieniem przyczyny oraz zależności między występowaniem krwotoku a wielkością i charakterem guza nadnercza.
2. Przedstawienie krwotoku nadnerczowego jako pierwszej manifestacji raka kory nadnercza oraz omówienie zasad diagnostyki różnicowej i przygotowania przedoperacyjnego u pacjentów ze zmianą krwotoczną w obrębie nadnercza.
3. Opracowanie i zaproponowanie algorytmu diagnostyczno-terapeutycznego w krwotoku nadnerczowym na podstawie przeglądu literatury i doświadczeń własnych, obejmującego zasady diagnostyki obrazowej, endokrynologicznej oraz kwalifikacji do leczenia chirurgicznego z uwzględnieniem stanu ogólnego pacjenta i podejrzenia złośliwości zmiany.

Wnioski

Krwotok do nadnerczy stanowi rzadki, lecz potencjalnie zagrażający życiu stan kliniczny, wymagający szybkiego rozpoznania oraz interdyscyplinarnego postępowania diagnostyczno-terapeutycznego.

Kluczowym elementem postępowania terapeutycznego jest właściwe przygotowanie pacjentów do zabiegu, zwłaszcza w przypadku podejrzenia guzów chromochłonnych, w których nadmierne wydzielanie katecholamin wiąże się ze zwiększonym ryzykiem powikłań sercowo-naczyniowych. Zastosowanie blokerów α -adrenergicznych przed operacją znacząco poprawia bezpieczeństwo leczenia chirurgicznego oraz rokowanie pooperacyjne.

Jednym z najważniejszych czynników determinujących wybór metody leczenia operacyjnego jest stan hemodynamiczny pacjenta oraz ocena integralności torebki nadnercza. W badanej grupie chorych laparoscopia okazała się metodą bezpieczną i skuteczną u pacjentów stabilnych hemodynamicznie, z krwotokiem ograniczonym do torebki guza, niezależnie od jego wielkości. Z kolei w przypadkach przerwania torebki i rozległego krwotoku preferowano operację klasyczną, która zapewniała lepszą kontrolę pola operacyjnego i redukowałą ryzyko powikłań śródoperacyjnych.

Skuteczne leczenie krwotoków nadnerczowych wymaga ścisłej współpracy zespołów chirurgicznych, endokrynologicznych i radiologicznych. Decyzje terapeutyczne powinny być podejmowane z uwzględnieniem indywidualnego stanu klinicznego pacjenta oraz charakterystyki guza ze szczególnym naciskiem na etiologię guzów złośliwych. Uzyskane wyniki potwierdzają skuteczność laparoskopowej adrenalektomii w leczeniu krwotoków ograniczonych do torebki oraz potrzebę stosowania operacji otwartej w przypadku pęknięcia torebki.

Podsumowując, nieurazowy krwotok do nadnerczy należy traktować jako objaw wtórny, najczęściej związany z obecnością guza nadnercza, wymagający pełnej diagnostyki obrazowej i hormonalnej. Przedstawiony cykl publikacji stanowi istotny wkład w rozwój chirurgii endokrynologicznej, przedstawia bezpieczny dla chorego algorytm postępowania, podkreślając przy tym znaczenie właściwej kwalifikacji, przygotowania przedoperacyjnego oraz doboru techniki operacyjnej.

Piśmiennictwo

Spis piśmiennictwa jest dostępny na końcu każdej z trzech publikacji prezentowanego cyklu rozprawy doktorskiej.

Kopie prac

Huge Hematoma as First Manifestation of Adrenocortical Carcinoma: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1,2 Siavash Świeczkowski-Feiz
ABCDEF 1,2 Piotr Kaszczewski
AD 3 Remigiusz Gelo
ABCDE 1,2 Ewa Krajewska
ABE 1,2 Krzysztof Celejewski
ABCDE 1,2 Sadegh Toutounchi
AD 4 Urszula Ambroziak
ACDE 1,2 Ryszard Pogorzelski
ADE 1,2 Zbigniew Gałązka

1 Department of General, Endocrine, and Vascular Surgery, Medical University of Warsaw, Warsaw, Poland
2 University Clinical Center of the Medical University of Warsaw, Warsaw, Poland
3 2nd Clinic of Anesthesiology and Intensive Care, University Clinical Center of the Medical University of Warsaw, Warsaw, Poland
4 Department of Internal Diseases and Endocrinology, University Clinical Center of the Medical University of Warsaw, Warsaw, Poland

Corresponding Author: Piotr Kaszczewski, e-mail: piokasz1@gmail.com
Financial support: Medical University of Warsaw
Conflict of interest: None declared

Patient: Male, 38-year-old
Final Diagnosis: Adrenocortical cancer
Symptoms: Acute pain in right side flank
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic • Oncology • Surgery

Objective: Rare disease

Background: Adrenocortical carcinoma (ACC) is a rare malignancy associated with unfavorable prognosis. It is mainly diagnosed in the fifth or sixth decade of life. Symptoms of ACC are associated with hormonal activity, presence of metastases, and size of the tumor. The treatment and prognosis depend on the stage of the disease assessed with the ENSAT staging system.

Case Report: A 38-year-old White man was admitted to our department from the city hospital due to a huge hematoma of the right adrenal gland (130×100 mm). On admission, the patient's condition was stable, and no active bleeding or other complications were present. Therefore, initially, conservative treatment was performed. The control CT scan showed reduction of the hematoma (90×80 mm). Due to the unknown character of the tumor and the sudden onset of bleeding, the patient was prepared for elective surgery according to the pheochromocytoma surgery protocol. Following preparation, the patient underwent right-sided adrenalectomy. In the post-operative histopathological examination, adrenocortical carcinoma was diagnosed, which allowed the patient to receive appropriate oncological treatment.

Conclusions: There is currently no clear algorithm for the management of adrenal hemorrhage. A hemodynamically unstable patient requires urgent surgical treatment. Patients in good general condition should be prepared for early elective surgery.

Keywords: Adrenal Gland Neoplasms • Adrenocortical Carcinoma • Hemorrhage

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/937569>

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Background

Adrenocortical carcinoma (ACC) is a rare malignancy, with estimated prevalence of 1-2 cases in 1 million, associated with unfavorable prognosis. ACC is mainly diagnosed in the fifth or sixth decade of life, at a mean age of 55 years old. In about 60% of cases, ACC is a hormonally functional neoplasm [1-3].

Patients with ACC may be divided into 3 groups in terms of the clinical presentation of the disease. In the first group the symptoms are secondary to the excessive hormone production. The second groups of patients present mainly non-specific symptoms caused by the effect of the mass, including abdominal pain, fullness, or early satiety. The third group includes patients in whom the lesion was detected during imaging examinations performed due to other reasons (incidentaloma) [1,4,5].

Several features in imaging examinations can show the malignant character of the lesion, such as: irregular shape with poorly-defined borders, internal hemorrhages, necrosis, calcifications, density of the lesion >10 HU (Hounsfield units) in the computed tomography (CT), lack of or small areas of intracytoplasmic lipid in MRI (Magnetic Resonance Imaging) or rapid growth >2 cm/year [6].

The treatment of ACC is a complex process. The only curative approach is complete surgical resection of the lesion. There is still no consensus concerning the operation technique—conventional open surgery or laparoscopy. In other adrenal tumors, especially ones smaller than 6 cm, laparoscopy is the criterion standard. However, in ACC some experts prefer a conventional approach regardless of lesion size. Adjuvant therapies aim to reduce the recurrence rate. The prognosis depends on

the stage of the disease (proliferation index/staging), serum cortisol concentration, the completeness of the surgical resection, and introduction of adjuvant therapies. Five-year survival ranges from 16% to 40% but increases to 60% to 80% when the tumor is limited to the adrenal gland [6,7].

We report a case of a 38-year-old White man, in whom the adrenal hemorrhage (AH) was the first symptom of the ACC

Case Report

A 38-year-old White man was admitted to a city hospital due to acute, right-sided, localized, flank pain. He had no concomitant disorders. In his previous examination (abdominal ultrasound) there was no mention of any adrenal lesions. On admission, the patient was in a stable state, with blood pressure (BP) 135/80 mmHg, and without tachycardia. In the abdominal ultrasound examination, a large, retroperitoneal hematoma was diagnosed on the right side. The subsequent contrast-enhanced computed tomography (CT) scan confirmed a large (13×10 cm) retroperitoneal, right-sided hematoma secondary to the bleeding to the adrenal tumor. The patient was transferred to the Department of General, Endocrine, and Vascular Surgery of the Medical University of Warsaw.

On admission, the patient was in stable condition, with BP 130/80 mmHg, heart rate (HR) 80/min, hemoglobin (HGB) 11 g/dl, and red blood cells (RBC) 3.55 [10⁶/μL]. On the second day following admission, the control CT scan showed a 98×85×80 mm right-sided adrenal hematoma, with density of 55 HU, without features of active bleeding. Due to the undetermined character of the adrenal tumor, following the suggestions of the MDT (multidisciplinary team), the individually

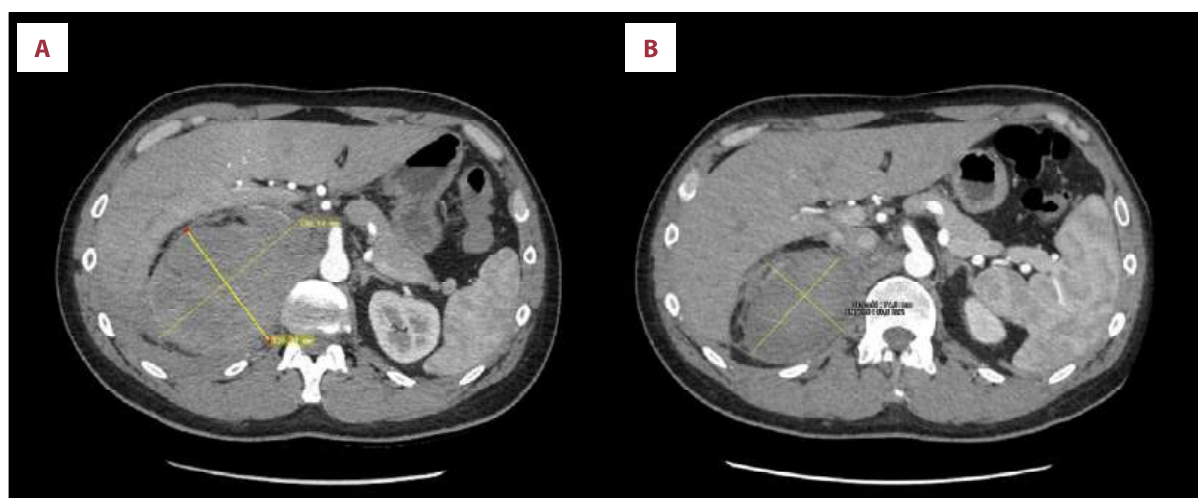


Figure 1. (A) Initial angio-CT scan of the abdominopelvic cavity shows the adrenal hematoma of 130×100 mm; (B) Angio-CT scan 3 weeks after the first examination shows decreased size of the hematoma to 90×60 mm.



Figure 2. Adrenal gland with hematoma after surgical excision. **a)** Adrenal gland with hematoma; **b)** Hematoma.

adjusted, maximal, well-tolerated daily dose of doxazosin of 8 mg (4 mg every 12 hours) was introduced. The laboratory tests results, which were available 3 weeks later, showed increased level of DHEA-S of 513.5 ug/dl, morning cortisol level 17.7 ug/dl, evening cortisol level 14.9 ug/dl, normetanephrine concentration 110.62 pg/ml (N<113.8 pg/ml), metanephrine concentration of 11.84 pg/ml (N<88 pg/ml), and very low methyltyramine level below the testing method sensitivity threshold.

During this 3-week period, the patient had an angio-CT scan of the abdominopelvic cavity performed, which showed decreased hemorrhage size to 90×60mm (**Figure 1**). Despite the decline in hemorrhage volume, the patient was not disqualified from surgical treatment.

After 25 days, the patient was admitted to our department again for an elective surgery. The patient was stable, with RR 135/90 mmHg, HR 90/min, HBC 13.80 g/dl, and RBC 4.77 [$10^6/\mu\text{L}$]. Due to the initially large size of the hemorrhage and expected difficult intra-operative conditions due to infiltration of the retroperitoneal space, we performed conventional open surgery with intraperitoneal approach. Intraoperatively, a large retroperitoneal infiltration encompassing the vena cava inferior and diaphragm was identified. After successful dissection of the hemorrhage from the infiltrating tissues, the adrenal gland, with initially identified adrenal capsule rupture (most probably secondary to hemorrhage), was successfully dissected and excised following the adrenal vessels ligation. All the excised tissues were sent for histopathological examination (**Figure 2**). The postoperative period was uncomplicated and the patient remained stable, with BP 120/75 mmHg, HR 80/min, HGB 10 g/dl, and RBC 4.29 [$10^6/\mu\text{L}$]. The patient was discharged from the hospital on the 4th day after surgery.

Histopathological examination revealed adrenal carcinoma with low proliferation and low mitotic index, 4 points according to the Weiss scoring system, and Helsinki score of 3.5 points (**Figure 3**). The necrosis was reported to be of vascular origin. Our patient is currently undergoing adjuvant chemotherapy with Mitotane and Cisplatin. The adrenal bleeding was the first manifestation of the adrenal carcinoma. No ACC was suspected in any previously performed examinations.

Discussion

In almost 60% of cases, ACC are hormonally active, in 30-40% it manifests with symptoms of Cushing syndrome, while another 20-30% of patients have hypercortisolemia and virilization of gynecomastia. In other cases, the diagnosis is related to effect of tumor growth or metastases to lungs (45%), liver (42%), lymph nodes (24%), and bones (5-20%).

In our patient, the performed hormonal tests did not permit diagnosis of ACC (DHEA-S 513.5 ug/dl, morning cortisol level 17.7 ug/dl, evening cortisol level 14.9 ug/dl, normetanephrine concentration 110.62 pg/ml (N<113.8 pg/ml), metanephrine concentration 11.84 pg/ml (N<88 pg/ml), and the very low methyltyramine level was below the testing method sensitivity threshold. Preoperatively, there was no basis for suspicion of a malignant process.

The treatment and prognosis depend on the stage of the disease assessed with the ENSAT staging system, which defines 4 stages of disease. Stage 1 (tumors <5 cm) and stage 2 (>5 cm) do not exceed the gland. Stage 3 extends into surrounding tissues (adipose tissue, lymph nodes), while in stage 4 distant metastases are present [6].

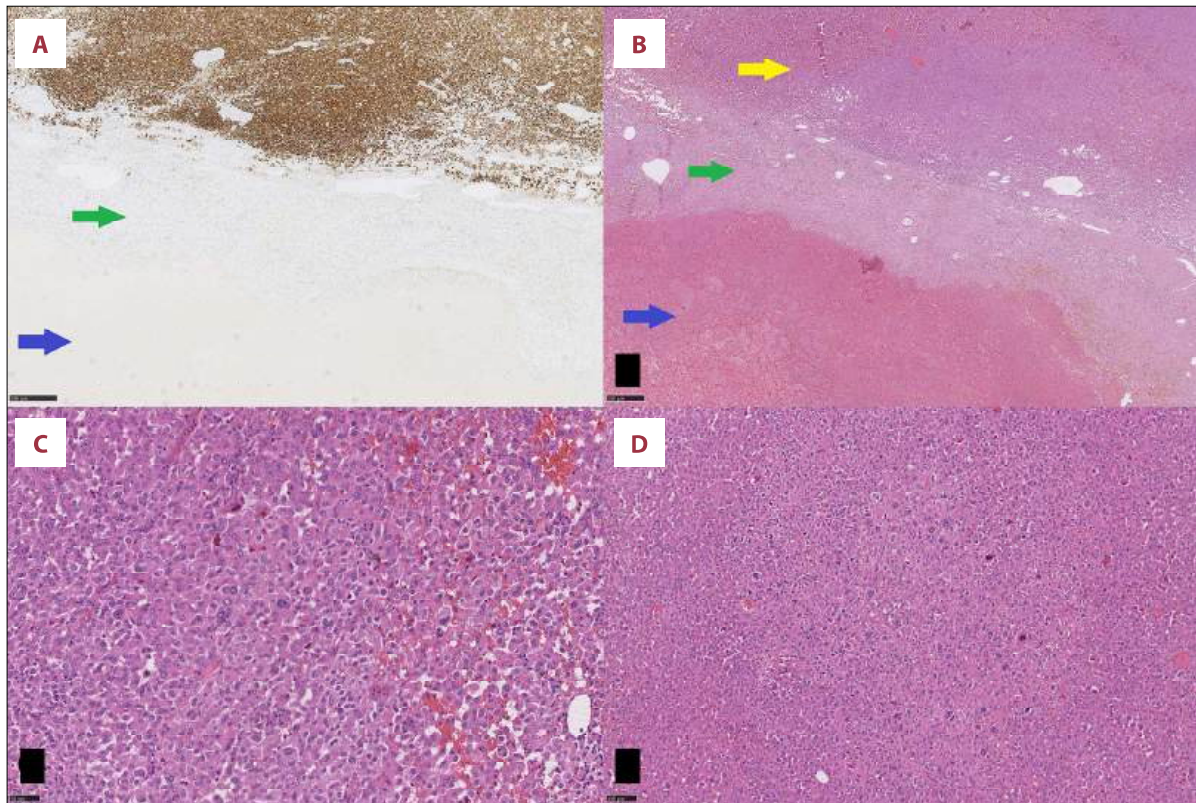


Figure 3. Postoperative histopathological examination. (A) (Hematoxylin and eosin staining) and (B) (immunohistochemical staining) were taken at low magnification and show hemorrhagic pseudocyst circuit in AAC, capsule, and hematoma content (yellow arrow indicates ACC, green arrow indicates the fibrous capsule, the blue arrow indicates blood and fibrine). (C, D) Show cells with compact, eosinophilic cytoplasm and nuclear pleomorphism (focally high nuclear grade).

There is a consensus that laparoscopy is the preferred surgical approach for adrenal tumors, but this is not the case with ACC, in which there are no clear guidelines concerning the selection of surgical approach. However, surgical excision with chemotherapy is associated with the best prognosis [2,6].

The role of laparoscopy in stage 1 and 2 ACCs, according to ENSAT, is questionable. Several authors suggest that lesions >6 cm should be treated with a conventional, open surgical approach, highlighting the increased risk of adrenal capsule rupture, local and regional recurrent lesions, or peritoneal metastases following laparoscopy. On the contrary, supporters of a laparoscopic approach stress the quicker recovery and faster introduction of adjuvant therapy after laparoscopy. They also point out that a less invasive intervention may be associated with lower risk of spread of carcinomatous cells in the peritoneal cavity. According to the ESE (European Society of Endocrinology), the ACC should be excised completely with surrounding adipose tissue. Simultaneous resection of the ipsilateral kidney is not recommended [6]. The adjuvant treatment is chemotherapy based on the Mitotane, Cisplatin, Doxorubicin, and Etoposide. Better long-term results

are reported in patients with small tumors in non-advanced stages, and in patients who received Mitotane immediately after surgical treatment.

In pathomorphological assessment, the Weiss score is most commonly used. It is based on: Fuhrman nuclear grade III/IV, mitotic rate >5/50 HPF, abnormal mitoses, percentage of clear cells, >1/3 diffuse architecture, presence of necrosis, venous invasion, sinusoid invasion, and capsular invasion. Each feature scores 1 point. Malignancy is diagnosed when the score is equal to or more than 3. The Helsinki score was developed to predict the prognosis and diagnose the metastasis of ACC. With the use of equation $3 \times \text{mitotic rate} (>5/50 \text{ high-power fields}) + 5 \times \text{presence of necrosis} + \text{proliferation index in the most proliferative area of the tumor}$, and a cut-off value of 8.5, the new scoring system can diagnose metastatic ACC with 100% sensitivity and 99.4% specificity [3,8-10].

In our patient the first and the only manifestation of the ACC was the intra-adrenal bleeding and consequent hemorrhage. There are very limited data in the literature concerning adrenal bleeding in adults and management in hemodynamically

stable patients. The need for surgical intervention in active bleeding resulting in hypovolemic shock is unclear.

The management of patients with adrenal hemorrhage in stable condition without features of active retroperitoneal bleeding remains debatable. The most common adrenal lesions are benign adenomas and pheochromocytomas. Taking this issue into account, in hemodynamically stable patients, emergency surgery should not be performed. Patient with adrenal hemorrhage who are hemodynamically stable, without features of active bleeding, should be prepared for early elective surgery as is typical for patients with adrenal tumor such as pheochromocytoma, the same for patients without adrenal hemorrhage. The pharmacological preparation should last about 2 to 3 weeks [7,11].

According to the NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors, pre-operative α -blockade is mandatory in patients with pheochromocytoma or paraganglioma (as are patients with normal levels of catecholamines) to minimize the intra-operative and perioperative risk by protecting against release of catecholamines due to anesthesia and surgical manipulation of the tumor [12]. Due to the unknown character of the lesion and to minimize perioperative risk, our patient's surgery involved a multidisciplinary team (MDT), including endocrinology specialists, with an individually adjusted daily dose of 8 mg doxazosin (4 mg every 12 hours).

In our patient, the hemorrhage was the only factor that influenced the decision about performing surgery. Laboratory tests and imaging examinations (CT, MRI) failed to show any signs of malignancy. The patient did not present with any other symptoms suggesting adrenal pathology. There was no suggestion of an adrenal lesion in his previous abdominal ultrasound examinations. The first suggestion of a malignant process appeared in the postoperative histopathological examination.

Therefore, our team finds it necessary to perform surgery in adult patients with adrenal lesion of an unknown or not clearly

defined character with bleeding of an unknown or undefined etiology. In our patient, it proved to be the first and the only symptom of malignant process – ACC.

Selection of the surgical approach should be individualized for each patient. The laparoscopic approach is feasible when bleeding is limited to the adrenal tumor. When the hematoma exceeds the adrenal tumor and is located in the retroperitoneal space, laparoscopy carries significant risk of damaging surrounding tissues or blood vessels. The hematoma also causes a local edema, which precludes clear identification of adrenal gland borders. In this situation, a conventional, open surgical approach seems safer because it allows for better visualization of the surgical field and anatomical structures. Due to the size of the hematoma, this approach was selected in our patient.

Conclusions

Adrenal bleeding may be the first and only manifestation of a malignant process, even at an early stage, when neither laboratory tests nor imaging examinations suggest a malignant etiology.

Our team finds it necessary to perform early elective surgery in adult patients with adrenal lesion of an unknown or not clearly defined character with bleeding of an unknown or undefined etiology, following standard 3-week pharmacological preparation.

Department And Institution Where Work Was Done

Department of General, Endocrine, and Vascular Surgery, Medical University of Warsaw, Warsaw, Poland.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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Characteristics of Adrenal Hemorrhage: A Single Clinic's Experience

Authors' Contribution:

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

Siavash Świeczkowski-Feiz^{1ABCEFG}, Sadegh Toutounchi^{1ABCDE}, Piotr Kaszczewski^{1CDF}, Ewa Krajewska^{1CDF}, Krzysztof Celejewski^{1CDF}, Remigiusz Gelo^{2CDF}, Ryszard Pogorzelski^{1EG}, Zbigniew Gałązka^{1EG}

¹Department of General, Endocrine and Vascular Surgery, University Clinical Center of the Medical University of Warsaw, Poland

²2nd Clinic of Anesthesiology and Intensive Care, University Clinical Center of the Medical University of Warsaw, Poland

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ABSTRACT:

Introduction: Adrenal hemorrhage (AH) is a very rare and potentially life-threatening disease which may be secondary to trauma or of non-traumatic etiology.

Aim: The aim of the study was to present the characteristics and management of adrenal hemorrhage and show that adrenal hemorrhage is more common than expected and that the clinical symptoms are not specific.

Materials and methods: This retrospective study involved 199 patients with postoperative diagnosis of adrenal hemorrhage.

Discussion: The factors identified as potential causes of adrenal hemorrhage are adrenocortical carcinoma, pheochromocytoma, and adrenal adenoma. The study group included 199 patients with postoperative diagnosis of AH. It showed that all patients with postoperative diagnosis had pheochromocytoma (n = 54), adrenal adenoma (n = 68), or adenocarcinoma (n = 17). If we look more careful at the results, we can find only 30% of patients (n = 39) with preoperative diagnosis of AH. This group of 39 patients was prepared for expedited surgery. In this group of patients, the preoperative diagnosis of AH was pheochromocytoma 28% (n = 11), adenocarcinoma (n = 4), and adrenal adenoma (n = 9).

Conclusions: Bleeding into adrenal tumors is still an insufficiently understood topic due to its unpredictability and, as can be seen in our material, of varying severity. Out of 199 patients, only 30% (n = 39) were prepared for surgery with a preoperative diagnosis of AH; most of them had pheochromocytoma. We suggest that is very important to prepare patients for surgery with a preoperative diagnosis of AH using α -adrenoreceptor antagonists. Prolongation of the diagnostic process (time between the imaging examination and the surgery) may result in the disease progressing and adrenal bleeding.

KEYWORDS:

adenocarcinoma, adrenal hemorrhage, pheochromocytoma

ABBREVIATIONS

ACC – adrenocortical carcinoma
AH – adrenal hemorrhage
CT – computed tomography
ESE – European Society of Endocrinology
HU – Hounsfield units
MRI – magnetic resonance imaging
SD – standard deviation
US – ultrasonography

INTRODUCTION

Adrenal hemorrhage (AH) is a very rare and potentially life-threatening disease which may be secondary to trauma or of non-traumatic etiology. Bilateral AH is an extremely dangerous and potentially lethal condition, which may lead to adrenal tissue destruction and primary adrenal insufficiency [1–3]. According to the literature data, stress (including severe systemic infection, septicemia, or extensive thermal burns), coagulopathy, birth trauma, and adrenal and idiopathic tumors can lead to AH, being non-traumatic causes of this condition. Among adrenal tumors, adrenocortical carcinoma (ACC), metastases to the suprarenal glands, and pheochromocytomas are the most common causes of AH [2, 4, 5].

Based on autopsy data, it is estimated that 0.14% to 1.1% of deaths, and up to 14% of deaths caused by hemorrhagic shock, are caused

by AH. The incidence of AH is seven times higher in the pediatric population and is followed by higher mortality in this population (i.e., Waterhouse-Friderichsen syndrome, usually involving severe bacterial infection caused by *Neisseria Meningitidis*, is featured with 55–60% mortality) [2, 6, 7].

The symptoms of AH are varied and non-specific; they depend on the intensity of the bleeding, the size of the hematoma, and the extent of adrenal tissue damage. Such symptoms as left or right flank pain, nausea, vomiting, asthenia, or confusion may be manifestations of other more common conditions, such as retroperitoneal hematoma or nephrolithiasis [2, 5, 8–10].

AH should always be taken into consideration and excluded in pregnant women with unilateral flank or back pains [11].

Contemporary imaging techniques, such as ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) allow for quick diagnosis of AH [5]. However, it is worth mentioning that there are diseases, such as melanoma metastases to the adrenal glands, that may mimic AH [3].

AIM

The aim of the study was to describe the symptoms of AH and its management, demonstrating at the same time that adrenal hemorrhage is a more common condition than might be expected

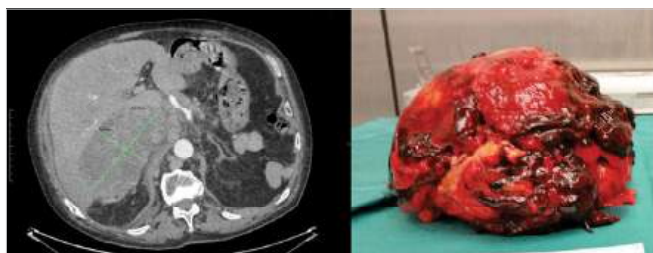


Fig.1. Preoperative diagnosis of adrenal hemorrhage in computed tomography angiography and the same tumor after operation.

that should be taken into consideration in case of the presence of various non-specific symptoms.

MATERIALS AND METHODS

Between the years 2012 and 2022 there were altogether 649 adrenalectomies in the Department of General, Endocrine and Vascular Surgery: 605 laparoscopic procedures and 44 open surgeries. In 199 cases there was a final diagnosis of AH, and in 39 cases it was confirmed with preoperative imaging examinations.

All patients with AH were initially treated or diagnosed in the Endocrinology Department and subsequently qualified for elective surgery. In 39 patients diagnosed with AH, elective surgery was performed after previous pharmacological preparation, either in the endocrinology department or on an outpatient basis. The mean time between release from the Endocrinology Department to admission to the Surgical Department was 40 days. In 160 patients, AH hemorrhage was diagnosed only on postoperative histopathological examination. The surgical method was adapted to the size of the tumor and the AH itself was not a determinant of the surgical method (laparoscopic or open).

RESULTS

The study group included 199 patients with a postoperative diagnosis of AH, 127 female (63.8%, mean age 58.83 ± 12.77 years) and 72 male (36.2%, mean age 57.46 ± 14.46 years). The data concerning the study group are presented in Tab. I. Analysis of the medical data shows that pheochromocytoma, ACC, and oral anticoagulants are connected with an increased risk of adrenal hemorrhage.

In the group of patients with postoperative diagnosis of AH, there were two subgroups. The first contains patients who were admitted to the emergency room with acute onset of right flank, left flank, or back pain. The second group consist of patients who – despite positive medical history of adrenal tumor – never got diagnostic of left or right back pain, abdominal pain after diagnosis of adrenal tumor, but the final diagnosis of adrenal hemorrhage was made on postoperative histopathological examination.

In the first group (39 patients: 20 females, aged 57.3 ± 16.55 years; 19 males, aged 55.15 ± 17.20 years), the most common diagnoses were pheochromocytoma ($n = 11$), adenoma ($n = 9$), and ACC ($n = 4$). The mean age of patients with pheochromocytoma was 50.8 years in women and 57 years in men; for those with adenoma, it was 38.4 years in women and 55.25 years in men; and in those with ACC it was 51.5 years in women and 47 years

in men. In our group, all patients were prepared for early elective surgery, due to the lack of preoperative diagnostics. None of our patients required emergency surgery. In the preoperative period, endocrinological workup for diagnosis of the hormonal activity of the lesion was carried out. The pharmacological preparation included the administration of alpha-blockers. According to the guidelines in Diagnosis and Management of Neuroendocrine Tumors, preoperative alpha-blockers are mandatory in patients with pheochromocytoma or those with normal levels of catecholamines to minimize the intraoperative and perioperative risk by protecting against the release of catecholamines due to anesthesia and surgical manipulation of the tumor. In this group, only 7 out of 39 tumors were diagnosed as hormonally active. However, this information was obtained postoperatively. It is worth emphasizing that with such a method of pharmacological preparation for surgery, there were no AH-related deaths in the perioperative or postoperative periods.

The second group consisted of 160 patients. In this group, the most common diagnoses were adenoma (36.74%, $n = 61$), pheochromocytoma (27.71%, $n = 46$), ACC (7.83%, $n = 13$), and metastases (7.23%, $n = 12$). This group, with extensive preoperative diagnostics of adrenal tumors, was prepared for surgery according to the preoperative diagnosis and in line with the endocrine surgery consensus and guidelines. In this group as well, there were no perioperative or postoperative deaths.

In both groups there were no significant differences concerning operation time (Tab. I, II.). The only difference was the preoperative pharmacotherapy. All patients without preoperative diagnosis of the lesion received alpha-blockers in preparation for the surgery. In the 160 patients with preoperative diagnosis, the pharmacological preparation depended on the type of the lesion: alpha-blockers were administered only to patients with confirmed pheochromocytoma and those with no clear diagnosis of the lesion type, which is in accordance with the guidelines in Diagnosis and Management of Neuroendocrine Tumors.

The data concerning the size and type of the tumors in our study group are presented in Tab. I.

In patients with pheochromocytoma or ACC, an increased risk of adrenal bleeding was observed in lesions greater than 54 mm and 51 mm, respectively. The pheochromocytomas measuring >60 mm accounted for 88% of all pheochromocytomas with preoperative diagnosis of AH, while in the group without preoperative diagnosis, it accounted for 35.7% of all lesions. ACCs >60 mm accounted for 50% of all ACCs complicated with AH in the first group and 58.8% of those in the second group.

In the first group, in whom AH was the first manifestation of the disease, nine patients did not have a preoperative diagnosis. This may suggest that hemorrhage caused the destruction of the adrenal tissue, preventing diagnosis.

The time interval from making the diagnosis of AH to surgical treatment varied. Patients with pheochromocytoma underwent at least two weeks of pharmacological preparation with doxazosin. Patients with suspicion of malignancy were operated on within one or two weeks of the initial diagnosis. Patients with preoperative diagnosis of AH but no clear diagnosis of the type of the lesion underwent two weeks' preparation with doxazosin.

Tab. 1. Postoperative histological diagnosis.

PARAMETER	ADRENAL ADENOMA (n = 68)	ADRENAL HEMATOMA (n = 7)	ADRENAL HYPERPLASIA (n = 13)	ADRENAL MYELOLIPOMA (n = 4)	ADRENAL PSEUDOCYSTS (n = 7)	ACC (n = 17)	METASTASIS (n = 15)	PHEOCHROMOCYTOMA (n = 57)	OTHERS (n = 10)	TEST	p-VALUE
Male	20.6% (n = 14)	85.7% (n = 6)	30.8% (n = 4)	25% (n = 1)	57.1% (n = 4)	35.3% (n = 6)	73.3% (n = 11)	36.8% (n = 21)	50% (n = 5)	Fisher	< 0.001
Female	79.4% (n = 54)	14.3% (n = 1)	69.2% (n = 9)	75% (n = 3)	42.9% (n = 3)	64.7% (n = 11)	26.7% (n = 4)	63.2% (n = 36)	50% (n = 5)		
n	68	7	13	4	7	17	15	57	10	Kruskal-Wallis	0.0027
Mean (SD)	61.34 (10.1)	45.43 (22.85)	66.54 (9.13)	61.75 (10.37)	62 (26.87)	51.94 (12.56)	61.73 (9.82)	54.84 (12.61)	58.3 (17.33)		
Median (Q1–Q3)	63 (57–68)	42 (26.5–63.5)	69 (63–72)	64.5 (59–67.25)	74 (46–80.5)	53 (39–60)	61 (57.5–67.5)	57 (45–64)	57 (49.75–64)		
Range	31–79	20–76	44–77	47–71	20–87	30–71	38–80	32–76	29–91		
n	68	7	13	4	7	17	15	56	10	Kruskal-Wallis	< 0.001
Mean (SD)	47.57 (17.43)	71.29 (59.29)	47.69 (17.28)	77.5 (16.58)	71.43 (37.61)	85.24 (40.6)	80.27 (29.14)	53.7 (26.04)	94.2 (67.9)		
Median (Q1–Q3)	45 (36.5–51.25)	57 (42.5–68.5)	50 (30–60)	80 (73.75–83.75)	60 (50–87.5)	80 (55–110)	75 (60–90)	52.5 (30–70)	90 (42.5–116.25)		
Range	13–95	20–200	17–75	55–95	25–140	32–180	48–160	13–120	22–240		
< 40	27.9% (n = 19)	14.3% (n = 1)	30.8% (n = 4)	0% (n = 0)	14.3% (n = 1)	11.8% (n = 2)	0% (n = 0)	37.5% (n = 21)	20% (n = 2)	Fisher	< 0.001
40–60	54.4% (n = 37)	42.9% (n = 3)	53.8% (n = 7)	25% (n = 1)	42.9% (n = 3)	29.4% (n = 5)	33.3% (n = 5)	26.8% (n = 15)	20% (n = 2)		
60+	17.6% (n = 12)	42.9% (n = 3)	15.4% (n = 2)	75% (n = 3)	42.9% (n = 3)	58.8% (n = 10)	66.7% (n = 10)	35.7% (n = 20)	60% (n = 6)	Kruskal-Wallis	0.0438
n	62	6	10	2	7	15	10	49	8		
Mean (SD)	8.89 (3.26)	7.5 (5.68)	8.7 (3.4)	9.5 (2.12)	6.86 (1.68)	10.87 (4.26)	10.7 (5.06)	8.84 (2.66)	11.12 (3.18)	Kruskal-Wallis	0.0131
Median (Q1–Q3)	8 (7–10)	7 (4–7.75)	8 (7.25–10.5)	9.5 (8.75–10.25)	6 (6–7.5)	9 (8–13)	9 (8–14)	8 (7–10)	11 (8.75–14)		
Range	4–22	2–18	4–16	8–11	5–10	6–20	5–20	4–17	7–15	Kruskal-Wallis	0.5996
n	61	6	10	2	7	15	10	47	8		
Mean (SD)	5 (1.53)	4.17 (3.87)	4.4 (1.84)	4.5 (0.71)	4.57 (0.79)	6.33 (2.44)	6.9 (3.14)	4.83 (1.56)	6.75 (3.2)		
Median (Q1–Q3)	5 (4–6)	3 (2.25–3)	4 (4–4.75)	4.5 (4.25–4.75)	5 (4.5–5)	6 (5–8)	7 (4.5–8)	5 (4–6)	6 (4.75–8.25)		
Range	3–9	2–12	2–9	4–5	3–5	2–11	3–13	1–9	3–13	Fisher	0.5996
Right	50% (n = 34)	50% (n = 3)	38.5% (n = 5)	75% (n = 3)	42.9% (n = 3)	58.8% (n = 10)	46.7% (n = 7)	64.3% (n = 36)	40% (n = 4)		
Left	50% (n = 34)	50% (n = 3)	61.5% (n = 8)	25% (n = 1)	57.1% (n = 4)	41.2% (n = 7)	53.3% (n = 8)	35.7% (n = 20)	60% (n = 6)	Fisher	< 0.001
Open	5.9% (n = 4)	28.6% (n = 2)	0% (n = 0)	0% (n = 0)	28.6% (n = 2)	58.8% (n = 10)	40% (n = 6)	12.3% (n = 7)	60% (n = 6)		
Laparoscopic	94.1% (n = 64)	71.4% (n = 5)	100% (n = 13)	100% (n = 4)	71.4% (n = 5)	41.2% (n = 7)	60% (n = 9)	87.7% (n = 50)	40% (n = 4)		

Tab. II. Preoperative histological diagnosis.

VARIABLE	PARAMETER	ADRENAL ADENOMA (n = 9)	ADRENAL HEMATOMA (n = 5)	ADRENAL PSEUDOCYST (n = 4)	ADRENOCORTICAL CARCINOMA (n = 4)	HYPERPLASIA (n = 3)	METASTASIS (n = 3)	PHEOCHROMOCYTOMA (n = 11)	TEST	P-VALUE
Sex	Male	44.4% (n = 4)	40% (n = 2)	75% (n = 3)	50% (n = 2)	33.3% (n = 1)	33.3% (n = 1)	54.5% (n = 6)	Fisher	0.9629
	Female	55.6% (n = 5)	60% (n = 3)	25% (n = 1)	50% (n = 2)	66.7% (n = 2)	66.7% (n = 2)	45.5% (n = 5)		
Age [years]	n	9	5	4	4	3	3	11	Kruskal-Wallis	0.9056
	Mean (SD)	60.33 (12.55)	54.6 (32.17)	58.75 (17.82)	58.75 (16.07)	47 (24.02)	56.33 (16.5)	54.64 (11.51)		
	Median (Q1–Q3)	62 (58–65)	70 (20–76)	64 (55.5–67.25)	60.5 (51.5–67.75)	55 (37.5–60.5)	61 (49.5–65.5)	56 (47–60.5)		
	Range	31–77	20–87	33–74	38–76	20–66	38–70	38–73		
Size of tumor with hematoma [mm]	n	9	5	4	4	3	3	11	Kruskal-Wallis	0.2043
	Mean (SD)	47.56 (22.18)	106 (65.8)	65 (23.8)	102 (57.29)	52.67 (10.21)	88.67 (54.05)	68.55 (26.92)		
	Median (Q1–Q3)	40 (29–59)	90 (70–140)	65 (47.5–82.5)	89 (65–126)	57 (49–58.5)	68 (58–109)	75 (46.5–89.5)		
	Range	22–90	30–200	40–90	50–180	41–60	48–150	22–100		
Size of tumor with hematoma [mm] – division	<40	33.3% (n = 3)	20% (n = 1)	0% (n = 0)	0% (n = 0)	0% (n = 0)	0% (n = 0)	9.1% (n = 1)	Fisher	0.2047
	40–60	44.4% (n = 4)	0% (n = 0)	50% (n = 2)	25% (n = 1)	100% (n = 3)	33.3% (n = 1)	27.3% (n = 3)		
	60+	22.2% (n = 2)	80% (n = 4)	50% (n = 2)	75% (n = 3)	0% (n = 0)	66.7% (n = 2)	63.6% (n = 7)		
	n	9	5	4	4	3	3	11		
Hospital stay [days]	Mean (SD)	9.78 (5.89)	9 (5.61)	6 (1.41)	11 (5.48)	5 (3.61)	9.67 (5.03)	7.27 (2.1)	Kruskal-Wallis	0.469
	Median (Q1–Q3)	8 (5–12)	7 (7–10)	6.5 (5.5–7)	11 (7.25–14.75)	4 (3–6.5)	9 (7–12)	7 (6–8)		
	Range	4–22	3–18	4–7	5–17	2–9	5–15	4–11		
	n	9	5	4	4	3	3	11		
Days after surgery	Mean (SD)	5.56 (2.24)	6 (4.06)	5 (1.63)	6.25 (3.3)	3 (1.73)	5.67 (2.52)	4.82 (1.08)	Kruskal-Wallis	0.6836
	Median (Q1–Q3)	5 (4–7)	5 (3–8)	5 (4.5–5.5)	6 (3.75–8.5)	2 (2–3.5)	6 (4.5–7)	5 (4–5)		
	Range	3–9	2–12	3–7	3–10	2–5	3–8	3–7		
	n	9	5	4	4	3	3	11		
Operated side	Mean (SD)	44.4% (n = 4)	60% (n = 3)	25% (n = 1)	25% (n = 1)	33.3% (n = 1)	66.7% (n = 2)	54.5% (n = 6)	Fisher	0.8761
	Left	55.6% (n = 5)	40% (n = 2)	75% (n = 3)	75% (n = 3)	66.7% (n = 2)	33.3% (n = 1)	45.5% (n = 5)		
	Open	11.1% (n = 1)	40% (n = 2)	25% (n = 1)	25% (n = 1)	33.3% (n = 1)	33.3% (n = 1)	9.1% (n = 1)		
	Laparoscopic	88.9% (n = 8)	60% (n = 3)	75% (n = 3)	75% (n = 3)	66.7% (n = 2)	66.7% (n = 2)	90.9% (n = 10)		
Operation time [minutes]	n	9	5	4	4	3	3	11	Kruskal-Wallis	0.4507
	Mean (SD)	122.78 (38.33)	113 (49.57)	115 (19.58)	132.75 (31.42)	123.33 (52.04)	155.33 (31.63)	148.64 (38.41)		
	Median (Q1–Q3)	140 (95–140)	120 (75–135)	117.5 (105–127.5)	135.5 (113.75–154.5)	140 (102.5–152.5)	165 (142.5–173)	150 (105–177.5)		
	Range	65–185	55–180	90–135	95–165	65–165	120–181	105–210		

The data concerning the surgical approach in relation to tumor size are presented in Tab. I. Fig. 1. shows the preoperative diagnosis of an adrenal hemorrhage in CT angiography and the same tumor after operation.

The surgeries we performed consisted of 81.4% (n = 162) laparoscopic operations and 18.6% (n = 37) classical operations. Laparoscopic operations were performed in tumors up to 40 mm in 92% (n = 46), in tumors 40–60 mm in 92.4% (n = 73), and in tumors over 60 mm only in 60.9% (n = 42) (Tab. I.). In our study group, there was no perioperative or postoperative mortality related to AH.

DISCUSSION

Characteristics of Adrenal Hemorrhage

AH is a life-threatening condition, especially in infancy. In adults, the clinical course of the disease is not connected with increased mortality, except in cases with hemorrhagic shock. In our study group, none of the patients with AH of non-traumatic etiology required emergency surgery. In two cases, a red-blood-cell transfusion was made due to reasons other than AH.

In the 10-year period, there were 199 histopathological diagnoses of adrenal bleeding in a total of 649 adrenalectomies (30.5%). In 39 patients, which is only 6% of all adrenalectomies, the AH was diagnosed preoperatively. Those patients required pharmacological preparation for surgery. All patients with preoperative diagnosis of adrenal bleeding reported flank or back pains. In 160 patients with histopathological diagnosis of AH, there was no evident correlation between the clinical symptoms and adrenal lesion.

Pathophysiology of Adrenal Hemorrhage

The adrenal gland is supplied in arterial blood by three arteries (the superior, middle, and inferior suprarenal arteries, which are branches of the inferior phrenic artery, the abdominal aorta, and the renal artery, respectively) [1, 2, 5, 12, 13]. The venous blood outflow is provided by a single adrenal vein. The adrenal cortex arterial blood supply is provided by numerous small arteries and it drains into a limited number of venules (this configuration is called a vascular dam). The large number of smooth-muscle cells situated in a longitudinal manner in the venous wall makes the vein susceptible to the influence of catecholamines. The excess of catecholamines causes a significant increase in vascular resistance and higher pressure and blood stasis in the adrenal glands. The decreased perfusion may result in small-arteriole ischemic necrosis, and after restoration of proper blood flow, can lead to AH.

Catecholamines cause platelets to aggregate and blood vessels to spasm. The adrenal vein wall structure facilitates its susceptibility to catecholamines, which may lead to adrenal vein thrombosis and weakening and rupture of the venous wall [12, 13].

In our study group, pheochromocytoma accounted for 28.6% (n = 57), metastases for 7.5% (n = 15), and ACC for 8.5% (n = 17) of all lesions. The correlation between these types of lesion and AH was the strongest; the AH was likely caused by degenerative lesions in the adrenal glands.

Imaging of Adrenal Hemorrhage

Imaging modalities in the diagnosis of adrenal gland pathologies include US, CT, and MRI. CT is the most commonly used for diagnosing AH. The morphological features of AH, such as the size, intensity, severity, and the presence of calcifications may suggest the etiology of the bleeding [10, 11, 13]. Acute AH has a radiodensity of 50–90 HU. In the vast majority of cases, conservative treatment of AH results in complete resolution within one year. Calcifications appear in the early stages of hemorrhage development, usually after one week [13, 14]. In our study group, the most common causes of AH included ACC (8.5%, n = 17), metastases to the adrenal glands (7.5%, n = 15), pheochromocytoma (28.6%, n = 57), and adrenal adenoma (34.2%, n = 68). Based on these observations, adrenal tumors with the features of AH should not be treated conservatively. In the overwhelming majority of cases, if the patient state is stable, early elective surgery should be performed, preceded by pharmacological treatment.

Management of a Tumor's Adrenal Hemorrhage

Bleeding to an adrenal tumor is a rare clinical condition and a non-invasive cause of adrenal hemorrhage. According to the literature data, it is most commonly observed in ACC, metastases to the adrenal glands, and pheochromocytomas [3, 11]. Every adrenal lesion should undergo mandatory assessment of the hormonal activity and potential malignancy. In the vast majority of cases, incidentalomas are benign, non-functional adenomas, but 5–8% of lesions are malignant. In our study group, ACC and metastases to the adrenal glands were the most common lesions in patients with AH confirmed in postoperative histopathological examinations.

In every patient without an apparent cause of AH, a thorough analysis of the imaging examinations should be conducted in order to differentiate between traumatic causes of bleeding or potential malignancy. AH may be the first and only symptom of adrenal lesion malignancy.

The overnight low-dose dexamethasone suppression test, the measure of urinary catecholamines or metanephrines, serum potassium, and – in hypertensive patients – upright plasma aldosterone/plasma renin activity ratio should be conducted during the diagnostic process [15].

Management of Adrenal Hemorrhage into Pheochromocytomas

Patients with AH secondary to pheochromocytoma should undergo early elective surgery preceded by pharmacological preparations. In order to achieve control of the symptoms of catecholamines, hypersecretion of α -adrenoreceptor antagonists (doxazosin) is used. When the treatment is accompanied with tachycardia, beta-blockers are administered (bisoprolol, metoprolol, or nebilein) [16–19].

Pharmacological preparation for surgery should be conducted in patients with and without blood pressure fluctuation; it should last at least 14 days. In some cases, blood pressure surge or cardiac arrhythmia appear during the induction of anesthesia, insufflation of the gas into the peritoneal cavity, or manipulation in the vicinity of the adrenal lesion. The lack of proper pharmacological preparation

for surgery may result in hypertensive crisis or cardiac arrhythmia, which may lead to potentially life-threatening complications [17, 19].

In our study group, 7 out of 39 patients (17.94% of the whole study group and 70% of patients with pheochromocytoma) with preoperative diagnosis of AH had elevated levels of methoxy catecholamines. In a study by Rzepka et al., in patients with hemorrhage due to a pheochromocytoma, both urinary and plasma catecholamines/metanephrines were elevated in 21 out of 24 patients (87.5%).

In pheochromocytoma, the adrenal tissue destruction secondary to adrenal bleeding may result in normalization of catecholamine secretion and resolution of its symptoms. It is doubtful, however, whether such a condition may be considered a self-healing process. Some pheochromocytomas may be asymptomatic and the hypersecretion of catecholamines and clinical symptoms may occur after a stressful predisposing factor such as surgery, injury, infection, or pregnancy. About 10% of pheochromocytomas are malignant lesions. In a small percentage of lesions, which are hormonally non-active, hormonal activity appears after a stressful factor [20].

Therefore, the decision to undergo surgery must be made individually for every patient. Laparoscopic adrenalectomy currently serves as the method of choice for patients in whom the AH is limited to tumor tissue and the lesion does not exceed 4–6 cm [19]. If the hemorrhage exceeds the tumor capsule, the laparoscopic surgery may be difficult to perform due to the inflammation of surrounding tissues in the retroperitoneal space and the complete excision of the adrenal tumor may be problematic. In such patients, conventional open surgery remains the treatment of choice.

Management of Adrenal Hemorrhage into Adrenocarcinoma

Adrenal hemorrhage may be the first manifestation of an adrenocortical carcinoma. Initial diagnosis of such lesions is based on the assessment of the hormonal activity and any potential malignancy features on CT imaging. It is worth pointing out that about 60% of ACCs are hormonally active [21]. In our study group, bleeding to the ACC was observed in 8.5% of all AH cases ($n = 17$). It is worth knowing that AH can be the first symptom of ACC [22].

The choice of surgical approach in ACC remains controversial. Some authors claim that a laparoscopic approach should not be used for the treatment of ACC due to the higher risk of rupturing the tumor capsule and the potential local spread of carcinoma or metastases to the peritoneum.

On the contrary, other experts regard the laparoscopic approach as feasible even in the treatment of adrenal malignancies, facilitating shorter recovery and shortening the interval between the surgery and adjuvant treatment. Those experts also stress that the less invasive procedure may feature a lower risk of malignant cells spreading in the peritoneal cavity. According to the ESE recommendations for the treatment of ACC, the tumor and surrounding adipose tissue should be completely excised. In our study group, 10 out of 17 ACC patients had conventional open surgery and in seven patients laparoscopy was performed.

Metastasis to the Adrenal Gland

Large autopsy studies have shown that the percentage of cancers which metastasize to the adrenal glands is about 42% for lung,

58% for breast, 16% for gastric, 10.3% for esophageal, and 14% for colorectal cancer and 50% for malignant melanomas. Metastases to the adrenal glands have also been reported for renal cell carcinoma, hepatocellular carcinoma, carcinoma of the bladder, lymphoma, seminoma of the testis, and osteogenic sarcoma. In patients who have an adrenal mass and an extra-adrenal malignancy, the frequency of this mass being metastatic ranges from 32% to 73% [18].

In our study group, in 7.5% ($n = 15$) of patients with AH, there was a hemorrhage to the metastatic lesion located in the adrenal gland. The detailed characteristics of metastatic lesions in our study group are presented in Tab. II.

Controversies in the Preoperative Management of Patients with Adrenal Hemorrhage

According to the guidelines for the management of patients with pheochromocytomas, both hormonally active and non-functioning, a minimum 10-day preoperative administration of alpha-blockers is recommended in order to minimize the perioperative risk [23]. A group of German surgeons do not use α -adrenoreceptor antagonists in the preoperative period. In their study, they claim that such pharmacological preparation is not connected with clear benefits to the patients [24]. On the contrary, our experience clearly shows that pharmacotherapy with alpha-blockers in the preoperative period increases the safety of the surgical procedure and minimizes the risk of complications during the surgery and in the perioperative period.

Operation Time

The average operation time in patients with AH was 120 minutes (90–150 min). The operation time in our study group was slightly shorter than that reported by Duralska et al. (130 min, SD = 42 min, 55–320 min) for patients without adrenal bleeding [22]. The detailed data concerning the operation time in patients with different postoperative diagnosis are shown in Tab. II. and Fig. 1.

Size of tumors with Adrenal Hemorrhage

The adrenal tumors are divided based on their size into three groups: < 4 cm, 4–6 cm, and > 6 cm. Adrenal bleeding is observed most commonly in the lesions < 4 cm and > 6 cm. Among the tumors measuring > 6 cm, AH is most commonly observed in pheochromocytomas (29%), adenomas (17.4%), ACC (6.4%), and metastases to the adrenal glands (6.4%).

The average size of the tumor with preoperative diagnosis of the AH was 7 cm.

CONCLUSIONS

Adrenal hemorrhage is still an underdiagnosed condition that should always be taken into consideration in the case of non-specific symptoms such as sudden back, flank, or abdominal pain. Prolongation of the diagnostic process (time between the imaging examination and the surgery) may result in the disease progressing and adrenal bleeding. Pheochromocytomas, ACCs, adrenal adenomas, and metastases feature a higher risk of adrenal hemorrhage.

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Corresponding author: Siavash Swiczowski-Feiz; Department of General, Endocrine and Vascular Surgery, University Clinical Center of the Medical University of Warsaw; Banacha street 1A, 02-091 Warsaw, Poland; E-mail: siavashfeiz@gmail.com

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Adrenal hemorrhage: diagnostics, management, and treatment. Review and clinical update

Siavash Świeczkowski-Feiz¹, Sadegh Toutounchi¹, Ewa Krajewska¹,
Krzysztof Celejewski¹, Remigiusz Gelo², Piotr Kaszczewski¹,
Wawrzyniec Jakuczun¹, Urszula Ambroziak³, Zbigniew Gałązka¹

¹ Department of General, Endocrine, and Vascular Surgery, University Clinical Center of the Medical University of Warsaw, Warszawa, Poland

² Second Department of Anesthesiology and Intensive Care, University Clinical Center of the Medical University of Warsaw, Warszawa, Poland

³ Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warszawa, Poland

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ABSTRACT

INTRODUCTION Adrenal hemorrhage (AH) is a rare and often underdiagnosed condition that can present with nonspecific symptoms and may be life-threatening. Accurate diagnosis and tailored management are essential.

AIM The aim of this paper was to review the literature on AH with emphasis on etiology, diagnostic approaches, management strategies, and methodological quality of available studies.

MATERIALS AND METHODS A structured search of the literature was performed. Forty-one relevant articles were included in the review. Risk of bias was assessed in 3 eligible studies (2 single-center series and 1 case series with literature review) using the Joanna Briggs Institute tools and adapted criteria.

RESULTS Trauma accounted for the majority of AH cases. Nontraumatic etiologies included anticoagulation, infection, stress, and adrenal tumors, such as pheochromocytoma, adrenocortical carcinoma, and metastases. Computed tomography and magnetic resonance imaging were the key diagnostic modalities. Management strategies ranged from conservative observation and embolization to laparoscopic or open adrenalectomy, guided by hemodynamic stability, capsule integrity, and suspicion of malignancy. All assessed studies had moderate risk of bias due to retrospective design and limited sample size.

CONCLUSIONS AH requires high clinical suspicion and structured imaging/endocrine evaluation. Open adrenalectomy is recommended in unstable patients, in the cases of capsule rupture, or when malignancy is suspected. In patients with hemorrhage confined to the adrenal capsule, laparoscopic adrenalectomy represents the preferred surgical approach. Larger prospective multicenter studies are warranted to establish standardized guidelines.

Correspondence to:

Siavash Świeczkowski-Feiz,
MD, Department of General,
Endocrine, and Vascular Surgery,
University Clinical Center of
the Medical University of Warsaw,
ul. Banacha 1A, 02-097 Warszawa,
Poland, phone: +48 22 599 25 64,
email: siavashfeiz@gmail.com

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INTRODUCTION Hemorrhage is defined as an acute loss of blood from a damaged blood vessel due to traumatic or nontraumatic causes.¹ Adrenal hemorrhage (AH) remains a diagnostic challenge because of its nonspecific clinical presentation.^{2,3} It is a rare but potentially life-threatening condition that can lead to acute adrenal insufficiency and may be fatal. Reported causes include septicemia, coagulopathy, bleeding diathesis, trauma, and adrenal tumors.²⁻⁴ Based on autopsy data, AH is estimated to occur in 0.14% to 1.1% of deaths. The pediatric population carries

a 7-fold higher risk of mortality from AH. In particular, Waterhouse–Friderichsen syndrome, usually associated with severe *Neisseria meningitidis* infection, is linked to 55%–60% mortality.^{3,5-7}

Clinical presentation of AH is heterogeneous and nonspecific. Symptoms depend on the severity of bleeding, the size of the hematoma, and the extent of adrenal tissue damage. Patients may present with abdominal pain, back pain (often misinterpreted as radicular pain), nausea, vomiting, hypotension, confusion, fever, or a hemoglobin (Hb) decrease by 1.5 g/dl or greater.^{3,8} Although

TABLE 1 Risk of bias assessment in the included studies

Author	Study type	Participant selection	Method (randomization / blinding)	Data reporting	Sample size	Overall risk of bias
Świeczkowski-Feiz et al ³	Single-clinic experience	Limited to 1 center	No randomization or blinding	Mostly complete	Small own cohort	Moderate ^a
Karwacka et al ⁴	Single-center experience	Limited to 1 center	No randomization or blinding	Mostly complete	Small own cohort	Moderate ^a
Marti et al ⁸	Case series + review (6 original cases + 133 cases from the literature)	Diverse sources, heterogeneous	No randomization	Inconsistent reporting	Small own cohort, large literature sample	Moderate ^a

a Risk of bias assessment was conducted for 3 clinical studies and all were classified as having a moderate risk of bias, which means that their findings are valuable and can be used to support clinical conclusions.

TABLE 2 Risk factors for adrenal hemorrhage^a

Conditions predisposing to adrenal hemorrhage		Examples
Trauma (80% of the cases)		–
Stress		Burns Hypotension Surgery (particularly orthopedic surgery)
Infectious disease		Sepsis caused by <i>Neisseria meningitidis</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Bacteroides fragilis</i> , <i>Streptococcus pneumoniae</i>
Medication		Anticoagulants Antiplatelets Nonsteroidal anti-inflammatory drugs Synthetic adrenocorticotrophic hormone Glucocorticosteroids
Hematologic disorders		Antiphospholipid syndrome Systemic lupus erythematosus Heparin-induced thrombocytopenia Other thrombocytopathies Thrombocytosis
Obstetric causes		Pregnancy Postpartum period Pre-eclampsia
Perinatal injury		Asphyxia Perinatal hypoxia Sepsis Fetal hematologic disorders
Adrenal gland tumor	Primary	Pheochromocytoma, adrenocortical cancer, myelolipoma, lipoma, hematoma, angioma, adenoma, pseudocyst
	Metastatic	Lung cancer, renal cancer, breast cancer, colon cancer, thyroid cancer, gallbladder cancer, melanoma
Gastrointestinal diseases		Acute pancreatitis

a Republished from Karwacka et al⁴ with permission under the Creative Commons CC BY-NC-ND license.

AH was historically diagnosed most often post-mortem, the increasing availability of computed tomography (CT) and magnetic resonance imaging (MRI) has led to more frequent incidental detection.^{3,9} Management strategies remain unclear and largely depend on the patient's clinical condition and the experience of the treating endocrinologist or surgeon. Hemodynamically unstable

patients may require intensive medical treatment, including blood transfusion, management of adrenal insufficiency, and surgical intervention, either laparoscopic or open.

AIM The aim of this review was to synthesize evidence on AH in adults, in terms of etiologies / risk factors, imaging-based diagnosis, and management strategies, as well as to identify gaps for future research.

MATERIALS AND METHODS Protocol and registration No protocol was registered for this review.

Eligibility criteria We included primary clinical studies (randomized or observational), case series (≥ 5 patients), and informative case reports on AH containing data on etiology, imaging, management, or outcomes. We excluded pediatric-only cohorts, non-English papers, and nonoriginal articles without extractable data.

Information sources The information was extracted from PubMed and Scopus, from 1990 to 2023. We also screened reference lists and relevant guidelines.

Search strategy Databases were searched using strings in the following format: ("adrenal hemorrhage" OR "adrenal hemorrhage" OR "adrenal bleeding") AND ("diagnosis adrenal hemorrhage/hemorrhage" OR "imaging adrenal hemorrhage/hemorrhage" OR "management adrenal hemorrhage/hemorrhage").

Selection process Two reviewers (RG and PK) independently screened titles / abstracts and full texts. Disagreements were resolved by consensus or by a third reviewer (JW).

Data collection process We extracted study design, setting, sample size, etiology / risk factors, imaging features, interventions (conservative, embolization, laparoscopic / open surgery), and outcomes (mortality, adrenal insufficiency, complications).

Data items Primary outcomes included all-cause mortality, hemodynamic instability, and need for

urgent surgery. Secondary outcomes comprised imaging characteristics across hemorrhage stages, distribution of tumor histologies, and endocrine activity.

Risk of bias assessment The risk of bias was evaluated using the Joanna Briggs Institute (JBI) critical appraisal tools for case series, with adapted criteria applied to case reports. For the study combining a case series with a literature review,⁸ relevant elements of the JBI tool were applied to assess methodological quality. All included studies were rated as having a moderate risk of bias, mainly due to limitations inherent to retrospective single-center designs, small sample sizes, and a lack of randomization or blinding (TABLE 1).

Statistical analysis Given the heterogeneity and predominance of case series/reports, a formal meta-analysis was not performed. Descriptive statistics (counts and proportions) were used where appropriate.

Ethics Ethical approval was not required for this systematic review of published literature.

RESULTS Study selection From the available literature, 41 articles were selected as relevant to AH, and included in the review. Among these, narrative reviews, single case reports without clinical outcomes, and purely imaging-focused articles were excluded from the risk of bias assessment. In total, 3 studies were included for detailed methodological appraisal: 2 single-center retrospective series^{3,4} and 1 combined case series with literature review.⁸

Study characteristics Trauma accounted for the majority (ca. 80%) of AH cases reported in the literature. Nontraumatic etiologies included anticoagulation/coagulopathy, sepsis/Waterhouse-Friderichsen syndrome, stress-related states, and adrenal neoplasms (pheochromocytoma, adrenocortical carcinoma, metastases). CT and MRI were the principal diagnostic modalities, with stage-specific imaging features consistently described.^{2,9,27}

Risk of bias The overall risk of bias in the included studies was determined as moderate, reflecting the limitations of retrospective, single-center designs, small patient numbers, and a lack of randomization or blinding.

Results of individual studies and synthesis Świeczkowski-Feiz et al³ and Karwacka et al⁴ reported clinical presentations and management outcomes of nontraumatic AH in single-center cohorts. Marti et al⁸ analyzed 6 original cases and 133 cases from the literature, providing insights into etiology, imaging characteristics, and treatment strategies (TABLE 1). Across the studies, management ranged from conservative care and selective embolization to laparoscopic or open

adrenalectomy, guided primarily by hemodynamic stability and capsule integrity.

DISCUSSION Anatomic and physiologic background The adrenal gland is supplied by the superior, middle, and inferior suprarenal arteries, branches of the inferior phrenic artery, abdominal aorta, and renal artery, respectively. This vascular configuration, known as a vascular dam, results in 50–60 small arterial branches that form a delicate subcapsular plexus around the zona glomerulosa. Consequently, the adrenal cortex is particularly susceptible to destruction during hemorrhage. Venous drainage occurs through a single adrenal vein, characterized by numerous longitudinally arranged smooth muscle cells in its wall. This unique structure makes the vein sensitive to catecholamines. Elevated catecholamine levels induce vasoconstriction, increased venous resistance, and blood stasis, predisposing the adrenal gland to ischemic necrosis of small arterioles and subsequent hemorrhage upon reperfusion. Catecholamines further promote platelet aggregation and vascular spasm, contributing to adrenal vein thrombosis under certain conditions.^{10–12,32}

Etiology and risk factors Trauma remains the strongest risk factor, responsible for approximately 80% of the reported AH cases. The remaining 20% were attributed to nontraumatic causes, including anticoagulant therapy, hematologic disorders, infectious diseases (eg, Waterhouse-Friderichsen syndrome), obstetric complications, perinatal injury, adrenal neoplasms (pheochromocytoma, adenoid cystic carcinoma [ACC], metastases), and gastrointestinal disorders.^{9,13–15} This broad spectrum highlights the need for high clinical suspicion, especially in patients with sudden abdominal, flank, or back pain without obvious trauma (TABLE 2).

Diagnostic imaging The diagnostic pathway for suspected AH includes ultrasound (US), CT, and MRI. US is often the initial modality in emergency settings, where acute hematomas appear solid and echogenic, later evolving into mixed echogenicity and eventually anechoic cystic lesions with possible calcified walls after 1–2 weeks. Doppler US demonstrates the avascular nature of hematomas.^{16,17,28}

CT remains the most widely used modality for confirming AH. Nontraumatic hemorrhage typically appears round or oval, with periadrenal extension if the capsule ruptures. Acute and subacute hematomas have radiodensity of 50–90 Hounsfield units, later evolving into organized pseudocysts with hypoattenuating centers and calcifications. In most cases, conservative management leads to complete resolution within 1 year. Calcifications appear in the early stages of hemorrhage development.^{16,17,28}

MRI provides the most detailed staging of AH based on Hb degradation products. In the acute stage (<7 days), intracellular deoxy-Hb yields

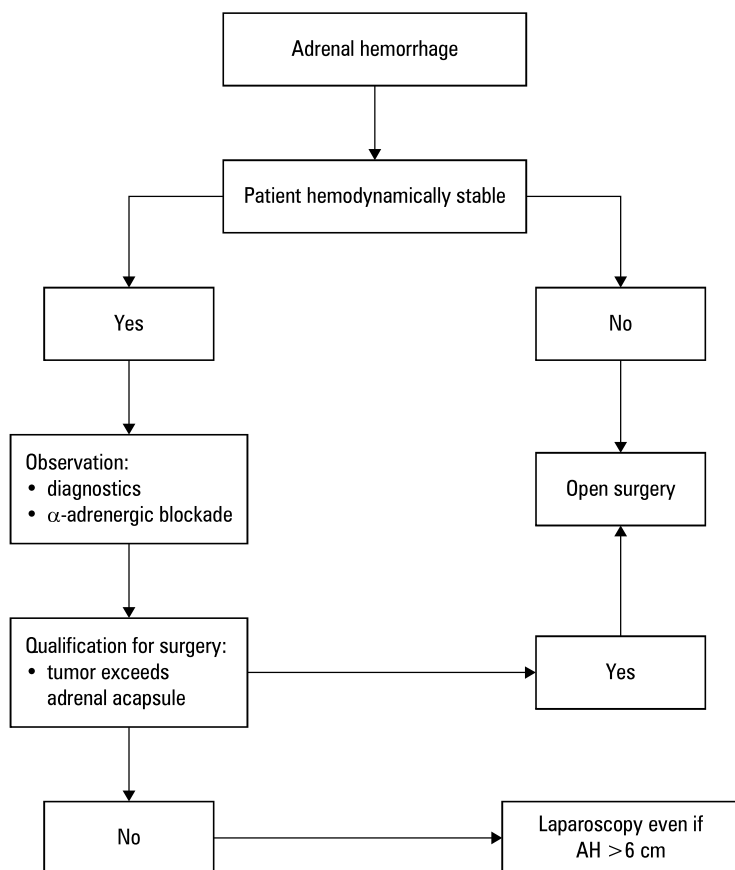


FIGURE 1 Management algorithm in adrenal hemorrhage (AH)

isointense to hypointense T1 signals and hypointense T2 signals.^{10,16,29} During the early subacute phase (2–7 days), intracellular met-Hb produces hyperintense T1 and hypointense T2 signals, initially at the periphery of the hematoma. By the late subacute phase (7–14 days), extracellular met-Hb is hyperintense on both T1 and T2 images.^{10,16,28,29} In chronic hematomas, hemosiderin deposition and fibrous capsule formation cause a hypointense rim on both sequences.^{10,16,28,29} A characteristic “train-track appearance” has been described in early nontraumatic AH, where the periphery enhances while the central portion shows low attenuation, resembling parallel railroad tracks.¹⁷ Recognition of this early sign may facilitate prompt diagnosis before hematoma formation is complete.

Histology and pathology Histologic evaluation confirms that pheochromocytomas are the most frequent hemorrhagic adrenal tumors, followed by ACCs and metastatic lesions. In a series by Świeczkowski-Feiz et al,³ 28.2% of hemorrhagic tumors were pheochromocytomas, 23.1% were ACCs, and 7.7% were metastases. Karwacka et al⁴ described 23 cases, with 9 involving surgical intervention. Histopathology confirmed adrenal hematoma, and 1 case demonstrated hormonal activity.

Marti et al⁸ analyzed 6 original and 133 literature cases, reporting pheochromocytomas and ACCs as the predominant hemorrhagic tumors, including cases with hormonal activity. Importantly, AH may be the first and only manifestation of adrenal malignancy, necessitating thorough endocrine and oncologic evaluation in all cases.^{3,4,9}

Management strategies Management depends on hemodynamic stability, capsule integrity, and suspicion of malignancy. In unstable patients or in the cases of capsular rupture, urgent open adrenalectomy is indicated to prevent catastrophic vascular or organ injury.¹⁵ In stable patients with contained hemorrhage, laparoscopic adrenalectomy is the gold standard, even for selected tumors exceeding 6 cm, provided surgery is performed in experienced centers.^{25–27} Reports indicate that large adrenal tumors (>10 cm) may also be safely removed laparoscopically without compromising oncologic outcomes (FIGURE 1).^{25–27}

Endocrine assessment is mandatory in all cases. Patients should undergo screening for pheochromocytoma with plasma free or urinary fractionated metanephrines.¹⁹ Cortisol excess should be excluded via the 1-mg dexamethasone suppression test, with further evaluation if abnormal.¹⁹ Primary aldosteronism should be considered in hypertensive or hypokalemic patients by calculating the aldosterone/renin ratio.²⁰ This structured approach, recommended by the Endocrine Society and European Society of Endocrinology, ensures accurate risk stratification of functional lesions.^{20–22,30}

Preoperative medical optimization is critical for pheochromocytoma. Both α-adrenergic blockade with doxazosin and β-blockade (if required) reduce perioperative risk.^{37–39} Despite adequate preparation, intraoperative hypertensive surges or arrhythmias may still occur during anesthesia induction, pneumoperitoneum, or tumor manipulation.^{37–39} Failure to reach pharmacologic optimization may result in life-threatening crises. Embolization has been reported as a temporizing option in selected cases, followed by definitive surgery.²³

Own experience and observations In our cohort, hemorrhagic adrenal tumors had a mean diameter of 7 cm. Hemorrhage was the first and only manifestation of underlying pathology in many cases.³ Histology confirmed ACC in 4 patients (1 hormonally active) and pheochromocytoma in 11 individuals, of which 5 were hormonally active. Interestingly, several pheochromocytomas were biochemically silent preoperatively, likely due to hemorrhagic necrosis masking catecholamine secretion. Operative times for laparoscopic and open adrenalectomy were consistent with published reports, with surgeon experience strongly influencing the outcomes. These findings reinforce the fact that every AH must be managed as a potential pheochromocytoma or ACC until histologically proven otherwise.³

Summary statement AH represents a diagnostic and therapeutic challenge due to its rarity, variable presentation, and diverse etiologies. Every AH occurring within a mass should be regarded as a possible pheochromocytoma or ACC until definitively excluded on histopathology.^{3,37} Preoperative endocrine evaluation and α -adrenergic blockade are mandatory. The choice of a surgical approach must consider tumor size, morphology, hemorrhagic dynamics, patient condition, and surgeon expertise.^{25,41,42} While laparoscopic adrenalectomy remains feasible for most contained lesions, open adrenalectomy is recommended in unstable patients and in the cases of capsule rupture with extracapsular bleeding.^{25,41,42} Ultimately, all patients with AH should be prepared for expedited surgery following comprehensive evaluation, as conservative management carries the risk of missing underlying malignancy.

CONCLUSIONS AH is a rare and underdiagnosed condition that should always be considered in patients presenting with nonspecific symptoms, such as sudden back, flank, or abdominal pain. Tumors, including pheochromocytomas, ACCs, and metastases carry a particularly high risk of hemorrhage. In the cases of hemorrhagic tumors with capsule rupture, laparoscopic surgery is associated with a significant risk of vessel or adjacent organ injury, and therefore open surgery is recommended. The timing of surgical intervention vs conservative observation remains debated in the literature; however, surgery should always be considered when histopathologic diagnosis is required.

Although laparoscopic adrenalectomy has become routine in surgical practice and offers well-documented advantages, such as shorter operative time, less postoperative pain, lower wound infection rates, and reduced risk of postoperative hernias in patients with hypercortisolism, these benefits apply primarily to contained lesions. In contrast, open surgery remains the preferred approach in the setting of capsule rupture or suspected malignancy.

Overall, AH management requires high clinical suspicion, structured imaging, and endocrine work-up. Treatment must be individualized according to hemodynamic stability, capsule integrity, and oncologic risk. Open surgery is indicated in unstable patients, suspected malignancy, or ruptured tumors, while laparoscopic adrenalectomy is feasible and safe in selected cases with contained hemorrhage.

ARTICLE INFORMATION

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Oświadczenia współautorów



Warszawa, 1/12/2025.
(miejscowość, data)

.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Świeczkowski-Feiz S, Toutouchi S, Kaszczewski P, Krajewska E, Celejewski K, Gelo R, Pogorzelski R, Gałązka Z. Characteristics of Adrenal Hemorrhage: A Single Clinic's Experience. Pol Przegl Chir. 2024 Apr 2;96(4):36-43. doi: 10.5604/01.3001.0054.4570. PMID: 39138988.

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.....
.....
.....

Mój udział procentowy w przygotowaniu publikacji określám jako...80.... %

Jednocześnie wyrażám zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świeczkowski-Feiz.....

.....
(podpis oświadczającego)

Warszawa, 1/12/2025.
(miejscowość, data)

3298738
Siavash Świeczkowski-Feiz
specjalista
chirurgii ogólnej

Warszawa, 1/12/2025.
(miejscowość, data)

.....
(imię i nazwisko)

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.....

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Jednocześnie wyrażám zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świeczkowski-Feiz.....

3298738
Siavash Świeczkowski-Feiz
specjalista
chirurgii ogólnej

.....
(podpis oświadczającego)


Siavash Świeczkowski-Feiz
specjalista
chirurgii ogólnej
.....
(imię i nazwisko)

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.....
.....
.....

Mój udział procentowy w przygotowaniu publikacji określam jako 80 %

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świeczkowski-Feiz.....


Siavash Świeczkowski-Feiz
specjalista
chirurgii ogólnej
.....
(podpis oświadczającego)

.....
(imię i nazwisko)

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Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świeczkowski-Feiz.....

S
Dr hab. n. med. Saadegh Toutounchi
specjalista chirurgii
ogólnej i nadciężności
4175058
(podpis oświadczającego)

Warszawa, 1/12/2025.
(miejscowość, data)

.....
(imię i nazwisko)

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Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świeczkowski-Feiz.....

S
Dr hab. n. med. Saadegh Toutounchi
specjalista chirurgii
ogólnej i nadciężności
4175058
(podpis oświadczającego)

Warszawa, 1/12/2025.
(miejscowość, data)

.....
(imię i nazwisko)

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Mój udział procentowy w przygotowaniu publikacji określę jako 3... %

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świczkowski-Feiz.....

.....
(podpis oświadczającego)
Dr hab. n. med. Saeed Toutounchi
specjalista chirurgii
ogólnej i naczyniowej
4475058

REMIGIUSZ GELO
(imię i nazwisko)

OŚWIADCZENIE

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Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świeczkowski-Feiz.....

Dr n. med. REMIGIUSZ GELO
lek. specj. anesteziologii i intensywnej terapii
189668
(podpis oświadczającego)

REMIGIUSZ GELO
(imię i nazwisko)

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Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świeczkowski-Feiz.....

Dr n. med. REMIGIUSZ GELO
lek. specj. anesteziologii i intensywnej terapii
189668
(podpis oświadczającego)

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Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świczkowski-Feiz.....

Dr n. med. REMIGIUSZ GELO
lek. med.
specjalista endokrynologii
i internisty
1690668

(podpis oświadczającego)

Ewa Krajewska
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Świczkowski-Feiz S, Toutouchi S, Krajewska E, Celejewski K, Gelo R, Kaszczewski P, Jakuczun W, Ambroziak U, Gałązka Z. Adrenal hemorrhage: diagnostics, management, and treatment. Review and clinical update. Wideochir Inne Tech Maloinwazyjne. 2025 Sep 26;20(3):255-260. doi: 10.20452/wiitm.2025.17981. PMID: 41209753; PMCID: PMC12590362. oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

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Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Siavasha Świczkowski-Feiz.....

Ewa Krajewska
(podpis oświadczającego)

Ewa Krajewska
(imię i nazwisko)

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Ewa Krajewska
(podpis oświadczającego)

Ewa Krajewska

OŚWIADCZENIE

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(podpis oświadczającego)

Piotr Kaszczewski
(imię i nazwisko)

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dr hab. n. med. i n. o zdr. Piotr Kaszczewski
LEKARZ
3167909
specjalista medycyny rodzinnej
(podpis oświadczenia)
D/1239/2018 O/1239/2020

Piotr Kaszczewski
(imię i nazwisko)

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LEKARZ
3167909
specjalista medycyny rodzinnej
(podpis oświadczenia)
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dr hab. n. med. i n. o zdr. Piotr Kaszczewski
LEKARZ
3167908
specjalista medycyny rodzinnej.....
(Stwierdzenie oświadczającego)
D/1239/2018 O/1239/2020