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REVIEW

SMALL CELL LUNG CANCER IN THE ERA OF IMMUNOTHERAPY

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ABSTRACT

Small cell lung cancer, accounting for approximately 14% of lung cancer cases, remains one of the most aggressive malignancies. Despite its lower incidence compared to non-small cell lung cancer, its early metastasis and rapid progression make small cell lung cancer a major public health concern due to poor survival outcomes. Five-year survival rates remain below 7% for extensive-stage disease, highlighting the urgent need for improved diagnostic and therapeutic strategies. Although epidemiologically small cell lung cancer is considered less hazardous than in previous decades, it continues to pose a substantial global public health burden. Changes in epidemiology include a narrowing of the historical male predominance, regional variations, and higher age-standardized incidence rates in Eastern Asia, Micronesia, Polynesia, Northern Europe, and North America. Although long-term survival remains limited, significant improvements with modern treatment options have been reported. Platinum-based chemotherapy combined with etoposide remains the first-line standard for both limited-stage and extensive-stage small cell lung cancer. Thoracic radiotherapy, prophylactic cranial irradiation to reduce the risk of brain metastases, and surgery for highly selected early-stage patients are among current treatment modalities, alongside second-line therapies such as topotecan. In parallel, novel therapeutic approaches primarily immunotherapies and patient-specific targeted therapies are showing substantial promise. The use of immune checkpoint inhibitors in combination with chemotherapy has been shown to improve survival in extensive-stage small cell lung cancer. Furthermore, integration of bispecific T-cell engagers targeting delta-like canonical Notch ligand 3, antibody-drug conjugates, poly-adenosine diphosphate ribose polymerase inhibitors, and epigenetic modulators with existing treatment strategies represents a promising direction for future therapy. Despite challenges including small trial sizes, resistance mechanisms, and treatment-related toxicity, these approaches may become more widely used in clinical practice. Overall, small cell lung cancer remains a serious clinical challenge that requires continued development of novel treatment strategies. These emerging approaches hold significant potential for providing more patient-specific therapeutic options. Ongoing and future clinical trials will be critical for establishing effective treatment algorithms and improving long-term outcomes in patients with this aggressive cancer. In this context, immunotherapy has emerged as a cornerstone of modern small cell lung cancer management, particularly in extensive-stage disease. Understanding the biological basis of immunotherapy responsiveness and resistance is therefore essential for optimizing current and future treatment strategies.

Keywords: Immunotherapy, prognosis, small cell lung carcinoma, therapeutics

INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women, being responsible for a quarter of all cancer deaths. Five-year survival is 59.0% for localized disease at diagnosis, and it decreases to as low as 5.8% for those with metastatic disease. Regarding that 57% of lung cancer cases in the United States are diagnosed after metastasis (1, 2), lung cancer poses a great danger to public health all around the world (1, 3). As a result, it is important to understand the classification and fundamentals of the disease (3, 4). It is divided into two main histological types: small cell lung cancer (SCLC) and non-SCLC (NSCLC) (Figures 1 and 2). According to the World Health Organization Classification of Tumors, SCLC is characterized by small, round-to-fusiform cells with scant cytoplasm, finely granular chromatin, and inconspicuous nucleoli (1). As the two types have different clinical behaviour, they need to be analyzed separately as well as together in order to optimize treatment options for both (3, 5). Although SCLC has a lower incidence compared to NSCLC, it is stated as the most aggressive type, which makes it important to specifically focus on it (5-7). Another aspect that should be examined is that given the limited durability of responses

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achieved with conventional chemotherapy and radiotherapy, immunotherapy has gained increasing attention as a strategy to improve long-term disease control. The integration of immune checkpoint inhibitors (ICI) into first-line treatment has marked a significant shift in the therapeutic landscape of SCLC (6, 7).

Epidemiology and Prognosis

Small cell lung cancer accounts for approximately 14% of all lung cancer cases, and it is expected to remain as a hazard to public health (6, 8, 9). Each year, nearly 250,000 patients are diagnosed with the disease, of which 200,000 are not able to overcome it (9). In 2019 global data, the disease is seen in females slightly more than males, with a difference of 5.1%. Although SCLC was seen dominantly in males in the past, due to the faster decrease of male patient cases, the male predominance of 68.3% in 1975 has changed through time. On the other hand, in females the incidence showed an increase until 1982 with a decreasing speed, and it started to decrease slowly afterwards (6, 9). Ancestry differences are present in SCLC cases as well with a notable difference from lung cancer cases in general. Despite the higher rate of lung cancer in general and the disadvantages of health service access, African ancestry is linked with a lower risk and higher survival rate of SCLC (8, 9). For both sexes, a high age-standardised incidence rate (ASIR) was seen in Eastern Asia, which states that the disease is seen at a higher rate regardless of the increase due to the increasing age. Additionally, a high ASIR was noted in Micronesia and Polynesia for males, in Northern Europe and Northern America for females (10). Regardless of age and sex, SCLC is still considered a public health danger and burden despite the decreasing trend of the disease overall.

The clinical presentation of SCLC is highly variable and often non-specific. The most frequently reported symptoms include cough, which is observed in approximately 40% of patients, and dyspnea, which occurs in around 34% of cases (Figure 3). Hemoptysis is less common, affecting roughly 10% of patients, yet it remains a notable presenting feature. Importantly, a substantial proportion of patients, estimated to be as high as 60%, may remain asymptomatic at the time of diagnosis, which contributes to delays in detection and initiation of therapy (11, 12). This silent clinical course is one of the major reasons why SCLC is typically diagnosed at an advanced stage. Nearly 70% of patients present with extensive-stage disease at initial diagnosis, underscoring the aggressive biology and rapid progression that characterize this malignancy (11, 13). Paraneoplastic syndrome (PNS) can also be existent in some cases of SCLC. Endocrinologic and neurological PNS are stated clinically with a significant amount alongside SCLC. SCLC is also one of the types of malignancies most strongly linked with PNS. Overall, the paraneoplastic entities associated with SCLC represent a complex interplay between ectopic hormonal secretion and immune cross-reactivity. This adds to the fatality and importance of possible treatments for SCLC. SCLC, which is strongly linked with smoking and tobacco carcinogens, is seen also as one of the most aggressive forms of cancer with a high capacity for metastasis (11, 12, 14, 15). Furthermore, use

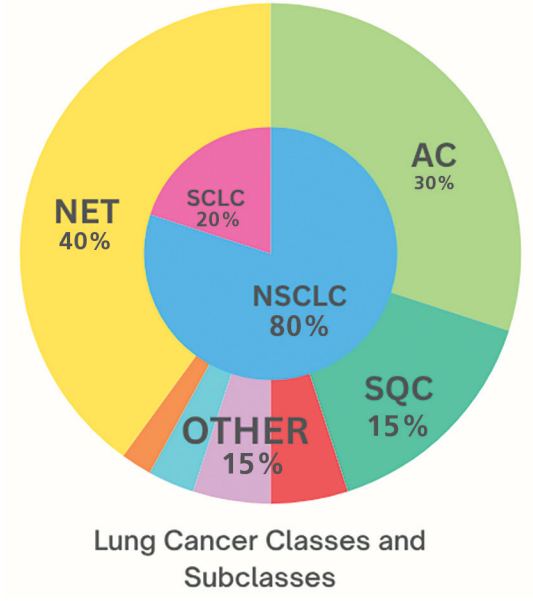

Figure 1: Showing the incidence of lung cancer classes and subsclasses. While adenocarcinoma and squamous cell carcinoma are mostly seen as subclasses under the class of only non-small cell lung cancer, the most common subtype neuroendocrine tumors can be considered both small cell lung cancer and NSCLC (9-11).
AC: Adenocarcinoma, SQC: Squamous cell carcinoma, NSCLC: Non-small cell lung cancer, NET: Neuroendocrine tumors, SCLC: Small cell lung cancer

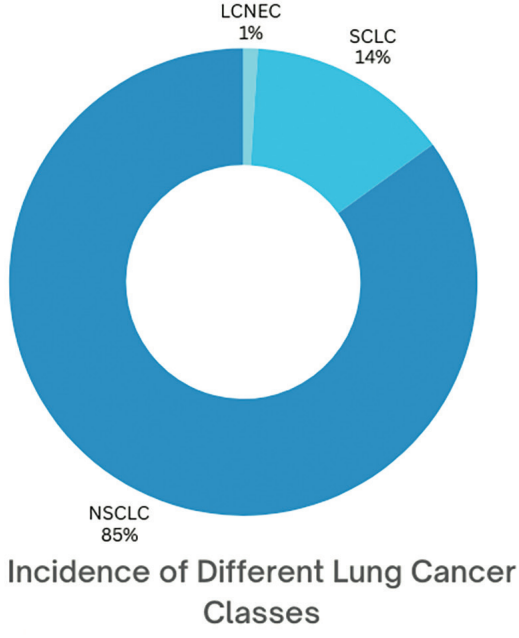

Figure 2: Showing the incidence pie chart of small cell lung cancer classes where non-small cell lung cancer is the most common type. Large cell neuroendocrine carcinoma corresponds to another class that is a minority compared to the other two sub-types (8, 10, 11).
NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer, LCNEC: Large cell neuroendocrine carcinoma

of tobacco can negatively impact the survival factors of the disease and it can make it harder for patients to get positive results from the treatments. The potential effects of tobacco use can be listed as genetic and epigenetic effects and chronic inflammatory responses which all combine to explain the aggressive biological behavior of SCLC and its tendency for early dissemination (12-15).

Even though SCLC is defined as a form of lung cancer with poor prognosis, it is seen that the prognosis of some SCLC cases was improving (14, 16). An increase in median age at diagnosis from 63 to 69 years and an improvement in five-year overall survival (OS) were also stated (16, 17). Specifically, one-year and five-year OS rates improved from 23% and 3.6% in 1975-1979 to 30.8% and 6.8% in 2010-2019 (17). A significant decrease in the incidence of the disease was stated as well, with a closer male-female ratio and a higher OS rate (18). These epidemiological shifts are largely attributed to declining smoking rates, reinforcing the well-established causal link between tobacco use and SCLC (15, 19). Advances in medical technology have contributed to reductions in incidence-based mortality; however, more effective systemic therapies are still needed to achieve substantial improvements in survival outcomes (19).

Low-Dose Computed Tomography for Lung Cancer Screening

Lung cancer, with its close association to smoking, is the leading type of cancer. Causing the majority of cancer mortalities, new methods to early-diagnose lung cancer have been subjected to trials. Previous randomized trials involving chest radiography and sputum analysis have shown no mortality reduction (18). However, low-dose computed tomography (LDCT) has allowed for a non-invasive, high resolution and practical screening test to be implemented. Due to the radiation exposure involved only people at high-risk are considered to be screened. The definition of high-risk, with little difference from guideline to guideline, is heavy-smokers aged 55 to 74 years of age who have a history of 30 pack-years of smoking. Former smokers who quit in the previous 15 years are also considered high-risk (20).

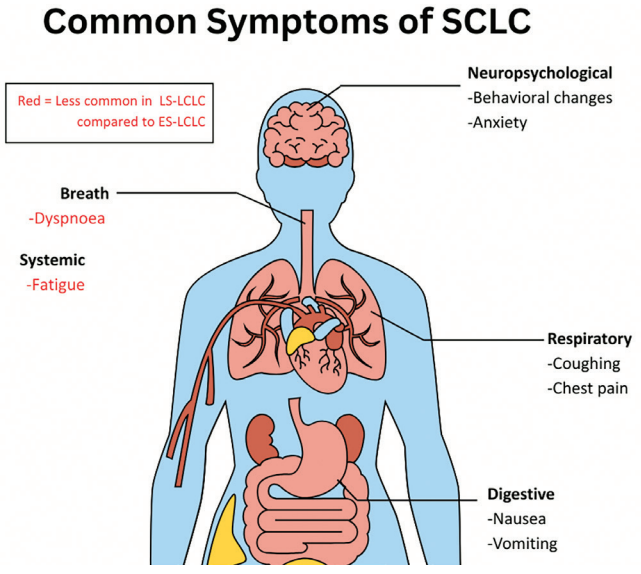

Figure 3: Showing signs and symptoms of small cell lung cancer. Symptoms written in red indicate symptoms that are more common in extensive stage compared to limited stage SCLC. Cough and dyspnoea were reported as the most common ones overall (12-15).
SCLC: Small cell lung cancer, LS: Limited stage, ES: Extensive stage, LCLC: Large cell lung carcinoma

A trial involving 12,773 participants (https://pubmed.ncbi.nlm.nih.gov/36428100/), was conducted to test the performance of a screening test. It had a high sensitivity and a low false positive rate. Most lung cancers were stage I or II with the majority being the stage I. This trial proved that screening can improve early detection in lung cancer. However, the SUMMIT trial could not evaluate the rate of overdiagnosis due to not having an unscreened control group (21). Overdiagnosis is an important aspect of screening. Treating a dormant or slow-growing cancer which won't be clinically significant in patients lifetime causes unnecessary and unwanted results (22).

The National Lung Screening Trial (https://clinicaltrials.gov/study/NCT00047385) conducted from August 2002 to 2004 had 53,454 participants which were considered high-risk for lung cancer. This study compared screening efficiency of chest radiography with LDCT. There were three screenings one year apart. Non-calcified nodules bigger than 4 mm were considered suspicious for lung cancer. The percentage of early stage cancers were higher in this study as well. In the LDCT group mortality rates were 20.0% lower than the radiography group but also LDCT had a higher rate of false positive results. SCLC had a lower detection rate compared to NSCLC by either screening procedure (23). Recently another study analyzing SCLC patients diagnosed at the Henry Ford Health System revealed that screen-detected patients had a considerably better OS rate (24). Ongoing trials will show if the benefits of LDCT screening outweighs its disadvantages.

Classification of Small Cell Lung Cancer

The Veterans Administration of Lung Study Group (VALSG) and the tumour, node, metastasis (TNM) staging of the American Joint Committee on Cancer are both used to classify SCLC. VALSG categorizes the disease as limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC) (25). TNM staging assesses the disease by the following: primary tumor (T), nodal involvement (N), and distant metastasis (M) (26).

If the disease is restricted to a single hemithorax and can be safely enclosed in one radiation field, it is considered to be limited. If the disease presents with malignant effusions of the pleura or the pericardium, or has spread beyond a single hemithorax, it is considered to be extensive (25). According to the 8th edition of TNM staging of lung cancer, T is assessed under the following categories: Tx, T0, Tis, T1 (T1a, T1b, T1c), T2 (T2a, T2b), T3, and T4. A tumor is considered Tx when the tumor does not show up in radiological or bronchoscopical

examination, but is evident in histopathological examination. T0 is defined as the absence of evidence of a primary tumor, and Tis refers to carcinoma in situ. Primary tumors are categorized into T1, T2, T3, and T4 stages based on their size, location, invasions of adjacent structures, and separate tumor nodules. Lymph nodules are assessed similarly and are categorized as the following: Nx, N1, N2, N3. If the lymph nodes are not suitable for assessment, the disease is Nx, and if there is no lymph node involvement, the disease is N0. N1, N2, and N3 stages are categorized depending on which nodules are involved. Distant metastasis is only divided as M0 and M1, no distant metastasis and the presence of it, respectively. Depending on how the patient presents in T, N, and M, they are diagnosed with stages from I to IV (26). Patients with stages I-III and suitable for curative intent therapy are equivalent to LS-SCLC, and stage III patients not suitable for curative intent treatment or stage IV patients are equivalent to ES-SCLC (27).

Chemotherapy in Small Cell Lung Cancer

For both LS-SCLC and ES-SCLC patients, platinum-based chemotherapy with the regimens cisplatin-etoposide or carboplatin-etoposide is recommended as a part of the first-line treatment (27). Although previously other regimens were used, a meta-analysis of 4,054 patients that compared the effectiveness of cisplatin versus non-cisplatin regimens concluded that the use of cisplatin regimens resulted in higher survival and response rates while not increasing toxicity (28). The effectiveness of cisplatin and carboplatin in patients diagnosed mainly with ES-SCLC was compared by Rossi et al. (29). Analysis revealed that both treatment arms had balanced OS, overall response rate (ORR), and progression-free survival (PFS) values. Hematologic toxicities were more common in the carboplatin arm, and non-hematologic toxicities were more common in the cisplatin arm, making the regimens' toxicity profiles an important deciding factor when administering these drugs (29). Another retrospective analysis concluded that cisplatin and carboplatin resulted in similar median OS for both ES-SCLC and LS-SCLC patients regardless of performance status. In LS-SCLC patients, the effectiveness of these drugs did not differ based on stage, and in both studies carboplatin was associated with better survival in older ES-SCLC patients (29, 30).

Role of Surgery in Small Cell Lung Cancer

When selecting patients for surgical resection, TNM staging is found to be of use (1). Although there is conflicting data when it comes to the benefit of surgery in SCLC, for a limited group of patients (T1T2N0), surgery with multimodality treatment may be recommended as a treatment option (Figure 4) (27). In a retrospective trial with propensity score matching, surgery was found to improve OS in all subgroups included, and it lacked significance only for the stage II subgroup. This improvement was especially seen in stage I and T1/T2N0 groups. They also found that if an R0 margin was not achieved in surgery, the positive results for OS were lost. It is also important to note that stage I and stage IIIA surgical resection patients who did not undergo adjuvant chemotherapy and radiotherapy performed poorer than their non-surgical counterparts (31). A meta-analysis including the aforementioned study also found a consistent and significant OS benefit for surgery when retrospective studies conducted after 2004 were analyzed (32). Similar to the mentioned study, surgery without adjuvant therapy did not have an OS benefit, and in both trials, lobectomy was associated with better survival when compared to other surgical practices (31, 32).

Implementation of Thoracic Radiotherapy in the First Line Treatment of Small Cell Lung Cancer

In 1992, two meta-analyses concluded the addition of thoracic radiotherapy (TRT) to chemotherapy resulted in improved survival (33, 34). Pignon et al. (33) found that the addition of TRT led to a 5.4% increase in the three-year survival rates; similarly Warde and Payne (34) reported an improvement in the two-year survival rates by 5.4%.

To test fractioned TRT's effect on survival, concurrently with the first cycle of platinum-based chemotherapy, 45 Gy TRT was given to participants either once-daily (1.8 Gy daily in 25 treatments) or twice-daily (1.5 Gy in 30 treatments). Two- and five-year survival rates were assessed, and five-year survival showed 10% pro-TRT margin, although two-year rates were not deemed statistically significant (35). However, when twice-daily treatment schedules were implemented as split-course, two- and five-year OS and PFS rates did not show a statistically significant difference, yielding similar results to once daily treatments (36). Although in both of these studies grade 3 esophagitis rates were high and seen more in the twice-daily treatment arms, in more recent trials these rates were found to be lower due to the use of modern radiotherapy techniques and positron emission tomography/computed tomography (CT) staging (33-40).

The CONVERT trial was designed to show that 66 Gy once-daily treatments would result in higher OS rates in comparison to 45 Gy twice-daily treatments (37). However, not only the survival rates did not show significance, but also the two- and five-year OS rates showed a 5% (56% vs 51%) and 3% (34% vs 31%) margin in favor of twice-daily treatments, respectively. With the high survival rates, low toxicity rates, and the fact that the trial was not designed to test equivalence in mind, the authors concluded that twice-daily TRT should continue to be the standard therapy (37). Initiated in the same year with the CONVERT trial, CALGB 30610 was also designed to test if high-dose once daily (70 Gy in 35 Gy once-daily fractions over seven weeks) treatments are superior to standard-dose twice-daily treatments (45 Gy in 1.5 Gy twice-daily fractions over three weeks). Although both treatment arms had similar OS rates at two- and five- years, the data lacked statistical significance and failed to show the superiority of once-daily treatment (38). On the contrary, in a recent phase III trial, 54 Gy high-dose hyperfractioned radiotherapy resulted in higher median OS (60.7 months vs 39.5 months), median PFS (30.5 vs 16.7), and two-year OS rates (76% vs 54%) in comparison

to standard treatment (39). These results were in line with the previous phase II trial comparing 60 Gy hyperfractioned TRT and standard therapy (40).

As individual trials favored one or the other, earlier or shorter admission of TRT versus longer or later admission of TRT was also researched in a 2016 meta-analysis. If TRT was administered before both the third cycle of chemotherapy and nine weeks after randomization, it was considered as early TRT. When compared to later or longer TRT, three- and five-year OS rates favored earlier or shorter TRT by 5.7% and 7.7% in trials with similar chemotherapy compliance in both arms. In trials with different chemotherapy compliance in both arms, it was reported that earlier or shorter TRT decreased survival. Similar to OS, PFS at three- and five-years also increased with earlier or shorter TRT in trials with similar chemotherapy compliance in both arms. Both hyperfractioned accelerated TRT and cisplatin-based chemotherapy were found to be more beneficial when TRT was delivered earlier or shorter, but this treatment plan resulted in an increased cardiotoxicity, neutropenia, and esophagitis (41). In the study done by Sun et al. (42), late TRT (starting with the third cycle of chemotherapy) showed comparable results to early TRT (starting with the first cycle of chemotherapy) in terms of complete response rate, OS, and PFS, but it showed an increase in intrathoracic rates without statistical significance. In this analysis, neutropenia was associated more with the early TRT arm, similar to the meta-analysis by De Ruysscher et al. (41, 42). The integration of TRT to current ES-SCLC treatment strategies is actively being researched in ongoing clinical trials (43). MATCH, a phase II trial, revealed that LD-TRT (15 Gy in five fractions) in combination with chemoimmunotherapy resulted in an ORR of 87.5%. Patients who were responsive to chemoimmunotherapy had a higher median depth of response (DpR) when compared to the whole cohort. Patients who achieved PR with a DpR above the median DpR rate had better OS and PFS, the three-year OS rates showing a ~39% difference. LD-TRT treatment was deemed tolerable with only 10.7% of patients discontinuing treatment due to adverse events (AEs); however, the authors noted that another phase II trial on concurrent radiotherapy (30 Gy in ten fractions), TREASURE, had to stop recruitment due to an imbalance in AEs seen in treatment arms (44). Therefore, the optimal dosage and fractionation of concurrent TRT treatment should be further researched. TRT treatment following chemoimmunotherapy was associated with improved OS and PFS and was considered to be tolerable in a recent retrospective analysis (43). Median OS was 21.67 months and 16.6 months for TRT and non-TRT arms, and one- and two-year OS rates also favored TRT treatment. Although higher doses of TRT were associated with higher rates of pneumonitis, TRT was not found to significantly increase any grades of AEs (44).

In a retrospective trial, ES-SCLC patients treated with combined therapy had longer median OS (18.1 months vs 10.8 months) and better PFS (9.3 months vs 6.0 months) compared to chemotherapy alone. TRT received within the six cycles of chemotherapy resulted in better local recurrence free survival (45). After propensity score matching the results still favored combined therapy; the median OS and progression free survival was 16.4 months and 7.9 months for Chtr/TRT and 11.6 months and 6.5 months for chemotherapy alone (45).

Immunotherapy in Limited-Stage Small Cell Lung Cancer

Whether LS-SCLC patients can benefit from immunotherapy is also actively being researched. Interim analysis of the ongoing ADRIATIC trial revealed that adjuvant durvalumab treatment after chemoradiotherapy led to significantly longer OS and PFS when compared to placebo in LS-SCLC patients without disease progression after first-line treatment. The incidence of grade 3-4 AEs was similar in both groups. Durvalumab did have a 8% higher incidence of pneumonitis or radiation pneumonitis, but grade 3-4 rates of this AE were similar at 3.6% and 2.1% (46).

Implementation of Prophylactic Cranial Irradiation in the First Line Treatment of Small Cell Lung Cancer

Prophylactic cranial irradiation (PCI) is a therapy offered to SCLC patients who are responsive to first-line therapy (Figure 4) (27). According to a meta-analysis, at three years, the incidence of brain metastasis was reduced by 25.3% and survival was increased by 5.4% due to the administration of PCI to SCLC patients (47). In this analysis, it was concluded that an increase in the dose resulted in a higher treatment success (47). However, when a total of 25 Gy in ten fractions was compared to 38 Gy in either 18 or 24 fractions, the high-dose treatment arm not only showed no significant benefit in decreasing the two-year incidence of brain metastases, but also decreased OS at two years and increased the incidence of intrathoracic metastases at two years (48).

In 2007, Slotman et al. (49) reported a decreased risk of brain metastasis and an OS advantage observed in the irradiation arm in a study with ES-SCLC patients. However, a study conducted in Japan found that PCI in patients with ES-SCLC did not improve OS, as the median OS was 11.6 months for PCI patients and 13.7 months for the control group. They attributed the difference in these two trials' OS results to the absence of magnetic resonance imaging (MRI) scanning of patients who didn't have symptomatic brain metastases, which might have resulted in asymptomatic patients getting included in the previous trial. The incidence of brain metastasis was lower in the treatment arm which is in line with the previous studies. At 6, 12, and 18 months, the PCI group had 15%, 32.9%, and 40.1% incidences of brain metastasis, these percentages were 46.2%, 59.0% and 63.8% in the control group (50).

The landmark meta-analysis by Auperin et al. (47) was also conducted in the pre-MRI era, and due to the lack of MRI surveillance, it is possible that patients with brain metastasis prior to PCI were also included in this analysis (51, 52). In two more recent studies conducted on LS-SCLC patients, both a baseline MRI and a restaging surveillance

before PCI was performed. PCI did not display a significant improvement in either PFS or OS rates (52-54). In another retrospective study with 1,068 LS-SCLC patients (648 after propensity score matching), PCI was found to significantly reduce brain metastasis rates while not having an effect on OS (55). One-, three-, five-year brain metastasis rates favored PCI compared to non-PCI groups (9.3%, 28.2%, 34.0% versus 27.5%, 38.5%, 40.3%). When one-, three-, five-year OS rates of PCI vs non-PCI groups were compared, this difference was not observed (86.6%, 49.4%, 39.9% vs 85.8%, 49.4%, 34.1%). Median PFS was also found to favor the PCI group (14.7 months vs 10 months) (55). Currently, there are three upcoming clinical trials comparing PCI vs only MRI surveillance in LS-SCLC patients and whose results are yet to be published (41).

In the immunotherapy era, the role of PCI warrants renewed evaluation. ICI may provide systemic disease control, including potential activity against micrometastatic central nervous system disease. In the MRI surveillance era, routine brain imaging enables earlier detection of asymptomatic brain metastases, raising questions about the risk-benefit balance of PCI, particularly regarding neurocognitive toxicity. The optimal integration of PCI, TRT, and immunotherapy remains undefined, and ongoing trials are expected to clarify whether MRI surveillance combined with systemic immunotherapy can safely replace PCI in selected patient populations (51, 52).

The role of PCI treatment in the era of immunotherapy is still not well-established. Ongoing trials such as SWOG 1827 MAVERICK and PRIMALung study, which compare MRI surveillance and PCI, are including patients who underwent immunotherapy; therefore, more clinical data on this matter will be available in due time. Currently, survival analyses of patients who underwent both chemoimmunotherapy and PCI are done with retrospective data. In a retrospective study, one-year intracranial metastasis rates were significantly lowered by ~40% in the PCI cohort, but there was no significant benefit observed for OS and PFS. Subgroup analyses revealed that PCI provided a statistically significant median overall survival advantage of 6.3 months to patients who achieved PR with first-line chemoimmunotherapy. Salvage radiotherapy showed similar survival outcomes to PCI; the only group PCI demonstrated a survival advantage in comparison to salvage radiotherapy was in the subgroup of patients who achieved PR (53).

Second Line Therapy in Small Cell Lung Cancer

Although SCLC is considered to be a chemotherapy-sensitive disease, second-line treatments hold an important role in SCLC treatment, as most patients tend to relapse after achieving complete remission in first-line chemotherapy (27, 56). Patients who show recurrence are categorized as resistant, sensitive, and refractory, depending on when the recurrence occurs (56). Resistant patients relapse less than three months after first-line treatment is over; if patients have a relapse after a longer time, they are considered sensitive, and if they relapse even before the initial treatment is over, they are considered to be refractory (52). Relapsed patients tend to have especially poor prognosis, but sensitive patients harbor the most potential when it comes to responding to second-line therapy (27, 55). Both topotecan and lurbinectedin are approved by the Food and Drug Administration, and are recommended as treatment options by the European Society for Medical Oncology guideline (27). Currently the European Union permits the usage of topotecan for second-line treatment of SCLC, and lurbinectedin is in orphan drug status (27). In different trials, topotecan was found to improve OS in comparison to best supportive care, and produced survival and response rates similar to those of cyclophosphamide, adriamycin, and vincristine (CAV) (57, 58). When compared with topotecan in patients with sensitive relapsed SCLC, carboplatin-etoposide rechallenge resulted in longer PFS (4.7 months vs 2.7 months); however, OS was similar for both treatment arms (59). The ATLANTIS trial compared OS in patients treated with lurbinectin + doxorubicin vs. topotecan or CAV regimens. For both treatment arms, similar OS rates were observed at 12, 18, and 24 months, and the primary endpoint of OS advantage was not met. Treatment-related AEs leading to treatment discontinuation and dose reductions and grade 3 or above hematologic toxicities were seen less in the lurbinectedin/doxorubicin group, in comparison to the control group (60).

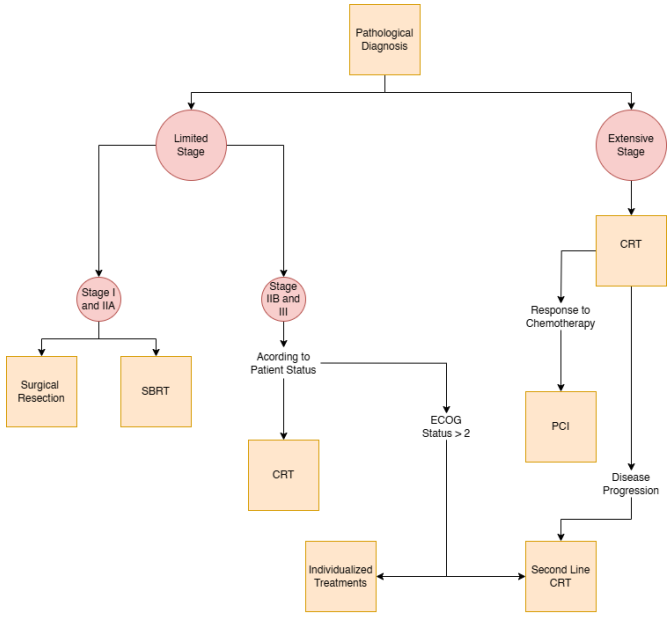

Figure 4: Showing the flowchart of diagnosis and treatment selection process used after the pathological diagnosis with emphasis on immunotherapy integration in first-line treatment for ES-SCLC, consideration of consolidative thoracic radiotherapy, and evolving roles of PCI and MRI surveillance in the immunotherapy era. Radiaiton based treatments such as prophylactic cranial irridation, stereotactic body radiation therapy and definitive concurrent radiation therapy along with surgery and individualized treatments are prefered acording to the patient response and disease progression (59-63).
SCLC: Small cell lung cancer, ES: Extensive-stage PCI: Prophylactic cranial irradiation, MRI: Magnetic resonance imaging, SBRT: Stereotactic body radiation therapy, CRT: Concurrent radiation therapy

Novel Therapeutic Approaches

The tumor immune microenvironment of SCLC is characterized by a highly immunosuppressive phenotype despite the tumor's high mutational burden. SCLC tumors commonly exhibit low major histocompatibility complex class I (MHC-I) expression, limiting effective antigen presentation to cytotoxic T lymphocytes. Additionally, the immune infiltrate is often dominated by immunosuppressive cell populations, including regulatory T-cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages with an M2-like phenotype. This immunological microenvironment contributes to limited immune recognition and represents a major barrier to effective immunotherapy responses (61, 63, 64).

Future therapeutic strategies in SCLC are increasingly focused on rational combination approaches, including immunotherapy combined with radiotherapy, deoxyribonucleic acid (DNA) damage response inhibitors, and epigenetic modulators. Emerging biomarkers such as tumor mutational burden, immune gene expression signatures, and circulating tumor DNA may enable better patient stratification and prediction of immunotherapy benefit (65, 66). In parallel, next-generation immunotherapeutic approaches, including bispecific T-cell engagers and personalized cellular therapies, hold promise for overcoming immune resistance and improving durable disease control (63, 64).

Due to its rapid progress, early-metastatic nature, ability to develop treatment resistance, and few therapeutic targets SCLC remains a hazardous and difficult disease to treat. New approaches in SCLC management are integrating immunotherapy with traditional chemotherapy (CT) and radiotherapy (RT), showing promise in their current situations. Most recently, combining ICI with chemotherapy has become the latest hot topic for SCLC. Different targeted therapies are also becoming more prominent. These novel therapeutic approaches are providing new combinations for SCLC treatment (Figure 5).

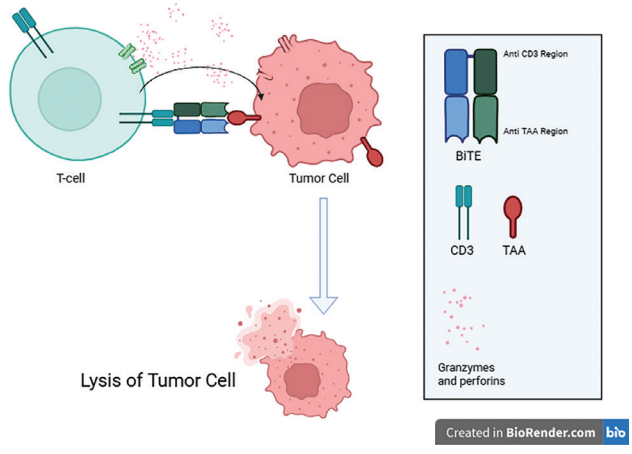

Figure 5: Showing the immuno-specific mechanism seen as a possible future treatment option. With antigen-antibody matchings, the lysis of tumor cells through the use of granzymes and perforins is seen as a mechanism with potential for less agressive and more efficient treatments (65-67).

Anti-Programmed Death-1/Programmed Death Ligand-1

In ES-SCLC patients, combining ICI with etoposide and platinum (EP) CT has proven its efficacy by improving OS and PFS rates. In contrast to CT-only treatments, combining atezolizumab with EP CT as a first-line treatment resulted in a two-month increase (12.3 months vs. 10.3 months) in median OS and almost a month increase (5.2 months vs. 4.3 months) in PFS, according to the IMpower133 trial (NCT02763579) (63, 64). Clinical trials have proved that using anti-programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors like atezolizumab and toripalimab provides notably improved results (64).

Antiangiogenic and Anti-Programmed Death-1

Combining an antiangiogenic (surufatinib) and anti-PD-1 agent (toripalimab) with an EP doublet regimen provided a new route for ES-SCLC treatment. This new regimen achieved tumor shrinkage in all of its patients. Combination therapy of surufatinib and toripalimab resulted in higher anti-tumoral activity whilst reaching clinically acceptable safety (63). Despite these improvements, only a subset of patients derives durable benefit, and resistance to immune checkpoint inhibition remains a major clinical challenge (63).

Bispecific T-cell Engager Molecules

Drugs targeting delta-like-ligand 3 (DLL-3) proteins on tumors are also emerging as a novel therapeutic approach. This new approach allows a T-cell mediated response against tumors. Bispecific T-cell engager molecules simultaneously connect to T-cells and tumor-associated antigens. This engagement provides T-cell activation and proliferation, ultimately leading to tumor shrinkage. Phase 2 clinical trial DeLLphi-301 (NCT05060016) findings show that tarlatamab, a new molecule, achieved significant tumor shrinkages on brain metastases in previously treated patients. In this trial tarlatamab exhibited an objective response rate of 40% in patients with relapsed/refractory SCLC. With long-term responses and adequate safety, tarlatamab is also a promising drug in treating SCLC patients (64, 65).

Poly-Adenosine Diphosphate Ribose Polymerase Inhibitors

Recent studies about poly-adenosine diphosphate ribose polymerase inhibitors (PARPi) have shown that RT with PARPi and anti-PD-L1 can be an effective treatment for SCLC. Olaparib, accompanied by RT, demonstrated cancer cell-specific radio sensitization in SCLC. Subsequently, anti-PD-L1 increases the anti-tumor effect by causing T-cells to infiltrate the tumor. This synergist radiosensitization effect can be utilized as a new combination therapy (66).

Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) are antibodies targeting cancer cells combined with chemotherapeutic agents. ADCs connect to their antigens and enter the cancer cells. After that, their chemotherapeutic agent exhibits its anti-tumoral effect. ADCs targeting delta-like ligand 3 (DLL3s) are still in development. ADCs' potential targets are DLL3, Seizure Related 6 Homolog, CD 276, and Tumor-associated calcium transducer 2. These are targets which are expressed widely in cancer cells (67).

Epigenetic Modulators

Epigenetic modulators aim to reprogram the genetic expression of the tumor cells and make tumor cells susceptible to chemotherapy and immunotherapy. The enhancer of zeste homolog 2 (EZH2) is a functional part of the polycomb repressive complex 2 (PRC2). PRC2, with its histone methyltransferase activity, regulates transcription and is highly expressed in SCLC. EZH2 methylates histones and silences tumor suppressor genes, promoting tumor progression. EZH2 inhibitors aim to suspend this process and improve cellular differentiation. While being early phase and preclinical epigenetic modulators like EZH2 may provide novel combination possibilities against SCLC (68, 69).

Challenges Against Novel Therapeutic Approaches

Even though new therapeutic approaches seem promising, they also have their own challenges. Due to their recent commencement, most of the studies are in early phases and they are conducted with small sample sizes. These studies need more randomized controlled trials in order for us to better understand them.

Resistance to immunotherapy in SCLC can be broadly categorized into mechanisms related to impaired antigen presentation, T-cell dysfunction, and immunosuppressive immune cell infiltration. Loss or downregulation of MHC-I expression reduces tumor antigen visibility, while chronic antigen exposure promotes T-cell exhaustion, characterized by sustained expression of inhibitory receptors such as PD-1. In parallel, the accumulation of immunosuppressive cell populations, including Tregs and MDSCs, further dampens effective anti-tumor immune responses. These mechanisms collectively explain both primary resistance and the development of acquired resistance following an initial response to immune checkpoint inhibition (70, 71).

Resistance is also a challenge in immunotherapy. Many tumors present primary and secondary resistance to ICI. With their unstable genome and heterogeneity, SCLC tumors are highly different genetically and epigenetically. If this genetic alteration is present before treatment and the tumor does not respond to treatment, then primary or adaptive resistance is observed. If a positive response is monitored, however gradually declines, this is reported as a secondary or acquired resistance. Secondary resistance is observed due to the suppression of drug responsive clones and proliferation of drug-resistant clones. Mechanisms of resistance are poorly understood (70).

Another challenge is the toxicity of novel therapeutic approaches. While new agents display promising effects, they also display similar toxicity profiles like their predecessors. Moreover immunotherapy combination therapies have a higher chance of adverse effects. This remains as a limiting factor (71).

Small cell lung cancer is characterized with its lack of predictive biomarkers. This deficiency causes challenges with personalized treatment. Newly studied biomarkers, which are targeted by different immunotherapy agents, make tailored treatment possible. These biomarkers also give information about resistance and side effects of immunotherapy agents (72).

Immunotherapy Resistance Mechanisms

The introduction of ICIs, particularly agents targeting the PD-1 and PD-L1 axis, has represented a significant therapeutic advance in the management of ES-SCLC. However, despite initial enthusiasm and modest improvements in OS when combined with platinum-based chemotherapy, the majority of patients derive limited or transient benefit from immunotherapy, underscoring the presence of both primary and acquired resistance mechanisms (70).

Although ICIs have proved some efficacy in SCLC treatment, a major portion of patients do not respond to treatment or have disease progression after an initial response. This is defined as "immunotherapy resistance" (73). After six months of ICI treatment, if there is disease progression or the best response of the treatment is stable disease this is considered to be primary resistance (74). Acquired resistance is defined as remission of disease after obtaining a objective response or progression after six months of stable disease (73).

Clinical success of ICIs in SCLC is limited compared to NSCLC. Although both cancers are related to high tumor mutation burden caused by tobacco exposure, their response to ICIs and resistance mechanisms have different natures. Also, SCLC differs from NSCLC in the aspect of tumor mutational burden. High tumor mutational burden usually means more T-cell infiltration and neoantigen presentation improving the efficacy of ICIs. In contrast, while having high tumor mutational burden SCLC tumors have immune desert phenotype (failing to cause an immune reaction) causing limited ICI efficacy (75). Tumor mutational burden and ICI response topic is giving us mixed results in SCLC. CheckMate 032 cohort and IMpower 133 cohort have given us mixed results. CheckMate 032 reported an association between high tumor mutational burden and improved outcomes. However, IMpower 133 reported no significant difference (70). These conflicting results indicate that tumor mutational burden alone is insufficient to predict response to ICIs in SCLC. High tumor mutational burden causes increased neoantigen formation and effective anti-tumor immunity requires intact antigen processing and presentation machinery. SCLC causes multiple tumor-intrinsic alterations limiting immune recognition despite this high mutational load.

Reduced MHC-I expression and defects in antigen processing hinder antigen presentation to cytotoxic T lymphocytes causing reduced immune activation. Therefore, high tumor mutational burden does not equal to enhanced T-cell infiltration or immune responses and contribute to primary resistance to ICIs (76). Impairment of the tumor's antigen presentation capacity is one of the fundamental mechanisms underlying resistance to ICIs. Cluster of differentiation 8^+ cytotoxic T-cells need tumoral neoantigens presented on the cell surface via MHC-I molecules. Beta-2-microglobulin, critical in the transport and stability of MHC-I, is indispensable in this process and loss of it can cause the antigen presentation to stop (77). Also decrease in expression of the transporter associated with antigen processing (TAP1/TAP2) proteins which carry peptides to endoplasmic reticulum causes decreased antigen presentation (78). Loss of heterozygosity at the human leukocyte antigen locus during treatment or tumor evolution, causes the tumor to lose its ability to present neoantigens (79).

In parallel, functional exhaustion of tumor-infiltrating T-cells undermines durable immunotherapy responses. Exhausted T-cells in the tumor microenvironment exhibit sustained expression of inhibitory receptors such as PD-1, TIM-3, and LAG-3, along with reduced effector cytokine production and proliferative capacity (70). Importantly, this exhaustion state may not be fully reversible with PD-1/PD-L1 inhibition alone, potentially explaining the modest survival gains observed in pivotal clinical trials (e.g. IMpower133, CheckMate 032) and supporting the exploration of combination strategies targeting multiple checkpoint pathways (77).

Small cell lung cancer subtypes exhibiting higher neuroendocrine phenotype (SCLC-A and SCLC-N) are associated with lower T-cell infiltration and lower MHC-I expression, therefore they are named "immune-cold". These subtypes have an epigenetic shield protecting them from immune recognition. SCLC-I subtype, associated with lower neuroendocrine attributes, has higher antigen presenting capacity and gives a better response to ICIs (77). Neuroendocrine phenotype and immune evasion are closely related to PRC2's subunit EZH2. EZH2 primarily trimethylates the lysine 27 on histone H3 and represses gene expression. EZH2 silences *MHC-I* and *TAP1* genes (70). This mechanism hinders the antigen presenting mechanisms and causes immune evasion. Also, EZH2 represses the expression of T helper 1 chemokines such as CXCL9 and CXCL10 which attract T-cells to the tumor site and causes T-cell exclusion (70).

In addition to tumor-intrinsic mechanisms, immunosuppressive immune cells contribute to immunotherapy resistance. Studies suggest that regulatory T-cells and MDSCs are highly available in SCLC tumors. They interrupt the anti-tumor activity through inhibitory cytokines like transforming growth factor beta, interleukin-10. These cells can limit the immune response and cause poor response to PD-1/PD-L1 blockade (76).

Several resistance mechanisms to immunotherapy have been extensively studied in NSCLC, whereas their relevance in SCLC is only beginning to be clarified. The unique neuroendocrine biology and immunosuppressive tumor microenvironment of SCLC may alter the expression and consequences of these pathways, suggesting that insights derived from NSCLC should be applied cautiously and supported by SCLC-specific evidence.

CONCLUSION

Small cell lung cancer's highly hazardous, malignant, and aggressive nature combined with its mostly limited long-term survival rate makes it a substantial research topic. Contemporary research is promising. New strategies are developed using immunotherapy combinations like combining ICI with chemotherapy or targeted agents. Although these approaches remain largely experimental, they represent important future directions for improving immunotherapy efficacy in SCLC. A better understanding of primary and adaptive resistance mechanisms will be significant to implementing new combinations and improving treatment effectiveness. In this context, immune-related factors such as T-cell exhaustion and immunosuppressive immune cells have gained attention, as they may contribute to reduced immunotherapy efficacy through inhibitory pathways and cytokine signaling. These new strategies are supported by discoveries of new biomarkers and new immunotherapeutic agents. Ongoing and future clinical trials will provide crucial information regarding these strategies and translate them into clinical tools that will improve survival and quality of life in SCLC patients. Integrating evidence with clinical trial data will help optimize treatment algorithms.

Ethics

Ethics Committee Approval: *This study involved a review of the published literature on the current and potential treatment options for small cell lung cancer with also a epidemiological perspective. As this was a secondary analysis of existing data, no new data were collected, and therefore, ethical approval was not required.*

Footnotes

Conflict of Interest: *The authors of this article, Kerem Günel, Nehir Özyedek, and Ahmet Onur Oğuz, are members of the Editorial Board of the Turkish Medical Student Journal. However, they were not involved in any stage of the editorial decision-making process for this manuscript. The editors who evaluated this manuscript are from different institutions.*

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ORIGINAL ARTICLE

EXPLORING THE DIAGNOSTIC LIMITS OF CHATGPT: HOW FAR CAN A LARGE LANGUAGE MODEL GO IN HISTOPATHOLOGICAL IMAGE INTERPRETATION?

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ABSTRACT

Aims: Artificial intelligence's integration into pathology has accelerated with the adoption of digital workflows. Large language models like ChatGPT offer unique opportunities but have yet to be systematically evaluated in diagnostic image interpretation.

Methods: In this comparative study, 24 histopathological images representing various tissue types and pathological entities were evaluated by ChatGPT-4o mini and 15 experienced pathologists. The model was prompted with a standard diagnostic query without access to clinical information. Pathologists independently assessed the same images. Responses were categorized as correct, false positive, false negative, low-impact error, or no interpretation. Standard diagnostic metrics were calculated, and group comparisons were conducted using McNemar's test and Fisher's exact test. Interobserver agreement among pathologists was analyzed using Fleiss' kappa.

Results: ChatGPT-4o mini achieved an accuracy of 71.4%, with a sensitivity of 60.0% and a specificity of 77.8%. The average accuracy of pathologists was 89.8%, with 97.7% sensitivity and 87.1% specificity. Low-impact errors were more frequent with ChatGPT-4o mini (33.3%) compared to pathologists (6.9%). McNemar's test revealed a statistically significant difference in favor of pathologists. The interobserver agreement among pathologists was in the lower range.

Conclusion: While ChatGPT-4o mini demonstrated partial diagnostic capabilities, it underperformed compared to experienced pathologists. The absence of a clinical context likely impacted the results. Future artificial intelligence models integrating image analysis and clinical data may enhance performance. Despite limitations, the potential ChatGPT holds as a supportive diagnostic tool in pathology is highlighted in this study.

Keywords: Artificial intelligence, generative artificial intelligence, microscopy, pathology

INTRODUCTION

ChatGPT is an artificial intelligence (AI) virtual assistant launched in November 2022, with its applications in medicine rapidly expanding. The first Food and Drug Administration-approved AI application in medicine emerged in 2017 with software designed to detect diabetic retinopathy (1). More recently, large language models (LLMs) such as ChatGPT have gained attention for their potential applications in pathology and other medical fields. The advancement and widespread adoption of digital pathology have further facilitated AI integration into diagnostic pathology (2).

Unlike AI-driven image analysis platforms such as PathAI or Google Health AI, ChatGPT does not perform direct image interpretation. Instead, it provides text-based insights that may complement pathology assessments when combined with expert knowledge. Thus, the number of studies evaluating its potential in pathology is steadily increasing, highlighting the need for a systematic assessment of its capabilities and limitations (3-6). While ChatGPT demonstrates proficiency

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in certain specialized fields, such as bone pathology, its performance relies primarily on theoretical knowledge rather than direct image analysis (7, 8). Consequently, its practical application in diagnostic pathology remains constrained.

Moreover, limitations such as the lack of deep critical thinking and reasoning, as well as the inability to verify source reliability, necessitate cautious use. Expert validation remains essential (9). Additionally, ChatGPT's diagnostic accuracy is significantly influenced by the availability of contextual information; in the absence of clinical data, its performance in microscopic image analysis is markedly reduced (10).

Despite these limitations, ChatGPT has unique attributes that explain why it was chosen for the present study. It is the most widely known and most accessible LLM in medical and educational settings, with many clinicians and trainees already experimenting with its image-upload function, despite its limitations as a general-purpose tool not specifically trained for histopathological image analysis. This accessibility and widespread informal use created the rationale for our study: to systematically evaluate ChatGPT's diagnostic performance against experienced pathologists under controlled conditions.

Recent works illustrate the growing interest in this area. Vaira et al. (11) compared ChatGPT with experts in the analysis of oral mucosal lesions, reporting lower accuracy with ChatGPT than human specialists. Mazzucchelli et al. (12) assessed ChatGPT's diagnostic ability in glioma histopathology, with similar findings. In cervical cytology, Laohawetwanit et al. (13) confirmed that LLMs can function as supportive tools but cannot replace expert evaluation. In addition to empirical evaluations, conceptual discussions have questioned whether ChatGPT should have a role in medicine at all, emphasizing both its potential utility and its inherent limitations (14, 15). Together, these studies highlight the research gap our work addresses: to benchmark ChatGPT against trained pathologists in a structured, case-based design.

In this study, we evaluated the ability of AI to interpret microscopic images of human tissues and compared its performance with that of experienced pathologists.

MATERIALS AND METHODS

Ethics Statement

This study did not involve identifiable patient data. All histopathological images were de-identified archival cases and were used solely for research and educational purposes. According to institutional and international ethical guidelines, a formal approval from an ethics committee was therefore not required. All participating pathologists took part voluntarily and provided informed consent to contribute their diagnostic assessments.

Tissue Sample Selection

This study was designed to explore and assess the performance of an AI rather than to establish definitive clinical conclusions. This study analyzed static microscopic images of 24 tissue samples, categorized into four groups:

- **Normal tissue samples (n=6):** Ureteral wall, thyroid, prostate, gastric mucosa, gallbladder wall, colonic mucosa (Figure 1).
- **Non-neoplastic lesions (n=6):** Helicobacter pylori gastritis, fibrous dysplasia of bone, cystitis cystica, ulcerative colitis, chronic lymphocytic thyroiditis, Sertoli cell-only syndrome (Figure 2 a-f).
- **Benign tumors (n=6):** Intradermal nevus, meningioma, osteochondroma, pleomorphic adenoma, intraductal papilloma of the breast, tubular adenoma of the colon (Figure 3).
- **Malignant tumors (n=6):** Papillary urothelial carcinoma, mucinous carcinoma, adenocarcinoma of the prostate, renal cell carcinoma, squamous cell carcinoma, papillary thyroid carcinoma (Figure 4).

This study was designed to explore and assess the performance of a LLM rather than to establish definitive clinical conclusions.

Image Acquisition and Processing

All images were captured using a Leica DM1000 microscope equipped with an ICC50 camera and proprietary software. The magnification levels were selected based on the histopathological characteristics of each tissue, ensuring the

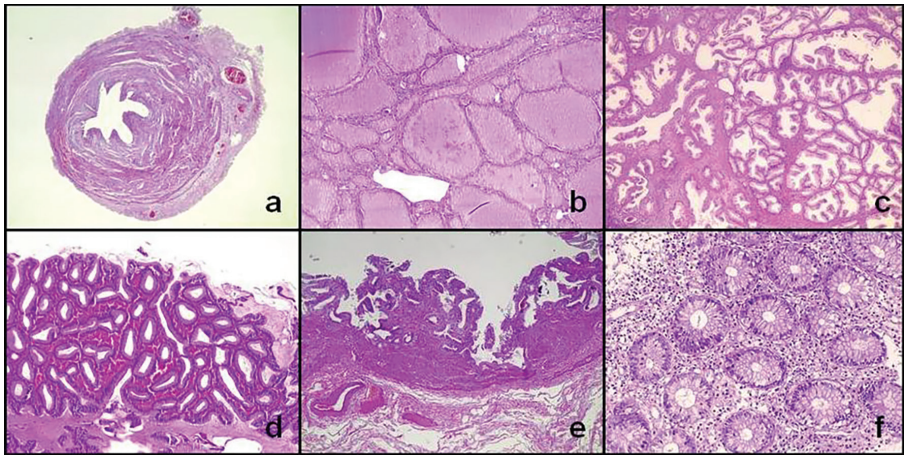

Figure 1: Normal tissue samples: A cross-section of the ureter showing the lumen and the ureteral wall (a), thyroid follicles (b), prostatic acini (c), gastric mucosa (d), mucosa and submucosa of the gallbladder (e), colonic mucosa (f).

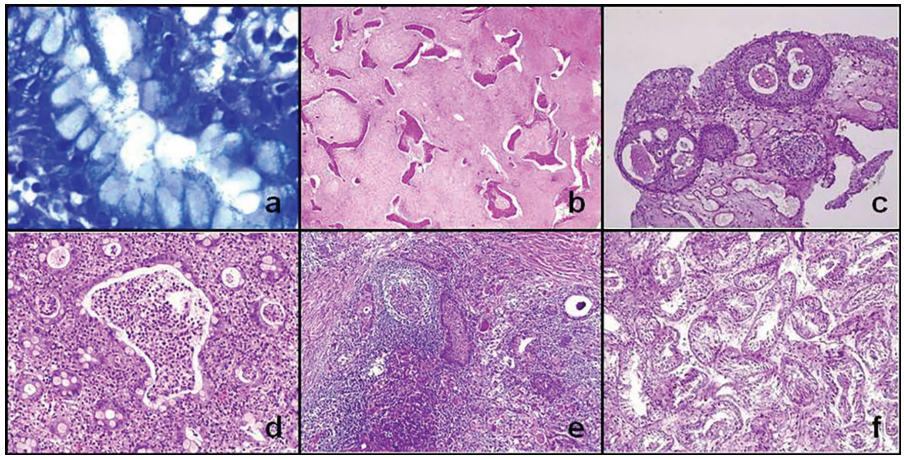

Figure 2: Non-neoplastic lesions: Helicobacter pylori gastritis (a), fibrous dysplasia of bone (b), cystitis cystica (c), ulcerative colitis (d), chronic lymphocytic thyroiditis (e), Sertoli cell-only syndrome (f).

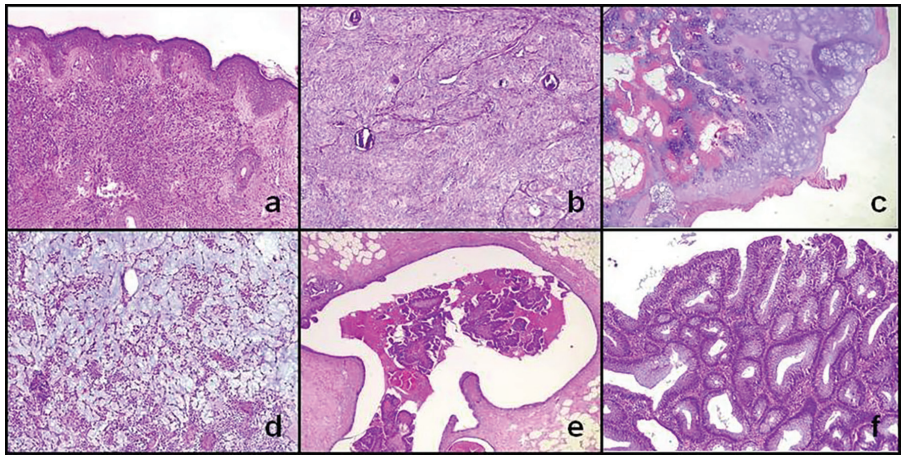

Figure 3: Benign tumors: Intradermal nevus (a), meningioma (b), osteochondroma (c), pleomorphic adenoma (d), intraductal papilloma of the breast (e), tubular adenoma of the colon (f).

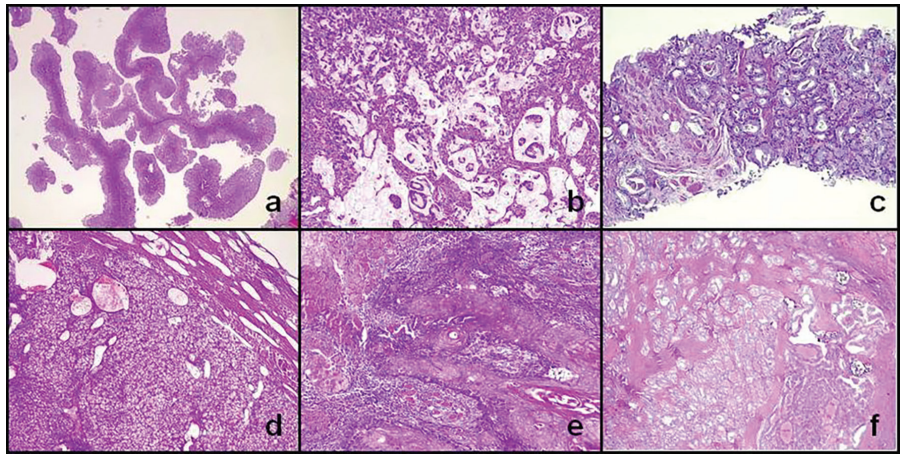

Figure 4: Malignant tumors: Papillary urothelial carcinoma (a), mucinous carcinoma (b), adenocarcinoma of the prostate (c), renal cell carcinoma (d), squamous cell carcinoma (e), papillary thyroid carcinoma (f).

most representative view. Images were saved in JPEG format, with a color depth of 24-bit and a resolution of 1600×1200 pixels at 96 dots per inch (both horizontal and vertical). No color correction or contrast adjustments were applied. All histopathological specimens originated from the same pathology department and were processed using identical tissue fixation, embedding, sectioning, and staining protocols to ensure methodological consistency across cases.

Evaluation by ChatGPT and Pathologists

The images were presented to ChatGPT-4o mini without any accompanying clinical information, and the model was prompted with the question "What is this?":

Responses of both ChatGPT and pathologists were categorized into five distinct categories:

- **Correct:** Accurate diagnosis or a partially correct response that aligned with the correct interpretation [true negative (TN) and true positive (TP) results].
- **Low-impact error:** Errors that did not significantly impact the patient's management, prognosis, or treatment (labeling a chronic inflammatory lesion as "reactive changes" instead of providing the exact clinicopathological entity, or misclassifying a benign neoplasm subtype without altering its benign nature).
- **False negative:** Failure to identify a lesion or classify it as benign when it was malignant.
- **False positive:** Incorrect classification of benign lesions as malignant.
- **No interpretation:** Inability to provide any meaningful diagnosis or classification.

The reference standard (ground truth) for each case was defined according to the original finalized histopathological diagnosis issued in routine diagnostic practice at the originating institution. Although participants evaluated only a single static microphotograph per case, the reference diagnosis had been established through comprehensive assessment of the entire specimen, including full slide review and clinical correlation when applicable.

As a control, the same microphotographs were independently evaluated by 15 pathologists with experience ranging from four to 23 years (mean: 11.25 years), also without clinical context. The inclusion of 15 pathologists was intended to reflect inter-individual diagnostic variability in routine practice rather than to optimize interobserver agreement metrics. Pathologists were eligible for inclusion if they had a minimum of three years of independent diagnostic experience. All participating pathologists were general surgical pathologists and did not have formal subspecialty training. They were recruited from multiple institutions, both national and international, ensuring a heterogeneous expert pool. To avoid observer bias, pathologists affiliated with the laboratory from which the cases originated were excluded from participation, and none of the participants had prior exposure to the evaluated samples. The diagnostic accuracy and error categories for each pathologist were recorded and classified using the same criteria applied to ChatGPT.

Statistical Analysis

Specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), and overall accuracy were the diagnostic metrics used to assess diagnostic performance. Only classifications labeled as TP, TN, false positive (FP), or false negative (FN) were included in the analysis. Cases with clinically insignificant errors or without any interpretation were excluded.

Diagnostic performance metrics for pathologists were calculated individually for each observer by comparing their classifications with the predefined reference standard. Subsequently, mean values and standard deviations were computed across the 15 observers to obtain group-level performance estimates.

For group comparison:

- Fisher's exact test was performed to assess overall differences in diagnostic accuracy between the model and the pathologists.
- McNemar's test was used to evaluate case-level discordance in paired classifications.
- The pathologists' performance was calculated as the average across 15 independent evaluations per case.

In addition, interobserver agreement among the pathologists was assessed using Fleiss' kappa statistic, which measures the degree of agreement beyond chance among multiple raters. Two analyses were conducted:

1. A full categorical model including correct diagnoses, incorrect diagnoses, and clinically insignificant errors.
2. A binary classification where both incorrect and minor errors were grouped as "incorrect".

A kappa value greater than 0.75 was considered to be excellent, a value between 0.40 and 0.75 was considered to be fair to good, and a value below 0.40 was considered to be poor agreement.

Statistical significance was determined by a p-value of less than 0.05. All analyses were conducted using Python (v3.11) and the Statsmodels library.

RESULTS

The correct response rate was 41.67% for ChatGPT-4o mini, compared with a significantly higher rate of 78.06% for pathologists. Among the pathologists, correct response rate ranged from 58.33% to 91.67%, indicating considerable variability in performance across evaluators. These calculations were based on case-specific diagnoses rather than a binary malignant-benign distinction (Table 1).

The error types made by ChatGPT-4o mini and pathologists were analyzed to assess their diagnostic tendencies. Low-impact diagnostic errors were observed in 33.3% of ChatGPT-4o mini's responses, in contrast to only 6.9% among the pathologists. Similarly, both FNs and FPs were observed in 8.3% of ChatGPT-4o mini's responses, while the corresponding rates for pathologists were 0.5% and 8.8%, respectively.

The frequency of no interpretation was comparable, with ChatGPT-4o mini providing no meaningful diagnosis in 8.3% of cases, compared to 5.5% for pathologists (Table 1).

Among the cases included in the study, lymphocytic thyroiditis (Figure 2e) proved to be the most challenging for the participating pathologists. Four pathologists (26%) did not provide an interpretation, nine pathologists (60%) classified the case as a malignant tumor, and only two pathologists (14%) reached the correct diagnosis. This difficulty can be attributed to the presence of squamous metaplasia in the image, a finding that is uncommonly observed in lymphocytic thyroiditis. These results indicate that, particularly when clinical information is limited, rare reactive histomorphological features may complicate interpretation and influence diagnostic outcomes.

Diagnostic Performance

The diagnostic capabilities of ChatGPT-4o mini and pathologists were evaluated across 24 cases, using standard performance metrics based on binary malignant-benign classification. Only valid classifications -TP, TN, FP, and FN- were included in the analysis; low-impact errors and uninterpretable cases were excluded.

ChatGPT-4o mini achieved a sensitivity of 60.0%, specificity of 77.8%, and overall accuracy of 71.4%. In contrast, the average performance of the 15 pathologists demonstrated a sensitivity of 97.7%, a specificity of 87.1%, and an accuracy of 89.8%. PPV and NPV followed a similar trend, with the pathologists outperforming ChatGPT across all metrics (Table 2).

These findings indicate a substantial performance gap, particularly in sensitivity and NPV, where pathologists showed perfect scores while ChatGPT-4o mini underperformed.

Statistical Comparison

Both case-agnostic and case-wise tests were conducted to assess if the differences between the two groups were statistically significant.

Fisher's exact test, comparing aggregated counts of correct and incorrect diagnoses, yielded a p-value of 0.191, suggesting no statistically significant difference when data were treated as independent observations. However, this independent-sample approach overlooks the paired nature of the diagnostic process, where the same cases were evaluated by both the model and the pathologists, thereby failing to account for case-specific correlations.

To account for this, McNemar's test was applied using case-level matched data, focusing on discordant classifications. This analysis revealed a difference between the two groups that is statistically significant ($p<0.001$), favoring the pathologists. Specifically, there were multiple instances where the model misclassified cases that the majority of pathologists diagnosed correctly. These findings underscore the importance of using paired statistical methods in diagnostic comparison studies and highlight the superior performance of the human experts in this setting. The results indicate that the model's misclassifications were not random but occurred systematically on specific cases that were correctly diagnosed by the pathologists.

Interobserver Agreement

The level of agreement among the 15 pathologists was evaluated using Fleiss' kappa statistic. When all three diagnostic outcomes were included - correct, incorrect, and low-impact diagnostic errors - the overall interobserver agreement was low, with a Fleiss' kappa of 0.13, indicating slight agreement. To assess whether diagnostic disagreement was driven by the presence of clinically insignificant errors, a binary classification was applied by grouping both incorrect and low-impact diagnostic errors as "incorrect". Even under this simplified dichotomy (correct vs. incorrect), Fleiss' kappa remained low at 0.14, suggesting that variability in pathologists' judgments persisted regardless of error type categorization. Importantly, diagnostic performance metrics were calculated by comparing each observer's classification against the predefined reference standard (original finalized diagnosis), rather than being derived from interobserver consensus.

Table 1: ChatGPT-4o mini's and pathologists' accuracy and error profiles.

Metric	ChatGPT-4o mini	Pathologists [mean ± standard deviation (range)]
Correct response rate (%)	41.67	78±10.9 (62.5-91.6)
False negative rate (%)	8.3	0.5±1.4 (0-4.1)
False positive rate (%)	8.3	8.8±6.2 (0-20.8)
Low-impact diagnostic errors (%)	33.3	6.9±4.9 (0-16.6)
No interpretation (%)	8.3	5.5±5.8 (0-16.6)

Table 2: Diagnostic performances of ChatGPT-4o mini and pathologists.

Metric	ChatGPT-4o mini	Pathologists [mean ± standard deviation (range)]
Sensitivity (%)	60.0	97.7±5.8 (83.3-100)
Specificity (%)	77.8	87.1±9.5 (68.7-100)
Positive predictive value (%)	60.0	75.1±14.7 (50-100)
Negative predictive value (%)	77.8	99.2±2.0 (94.1-100)
Accuracy (%)	71.4	89.8±6.9 (76.1-100)

DISCUSSION

Artificial intelligence has been rapidly transforming the field of pathology, particularly with the advent of digital pathology and whole slide imaging. AI-based systems have demonstrated their utility in detecting malignancies, identifying cellular atypia, and predicting prognostic factors. Studies have shown that convolutional neural networks can achieve high diagnostic accuracy in tasks such as identifying lymph node metastases in breast cancer and detecting prostate cancer in histopathological images (16, 17).

Moreover, AI models such as Google's DeepVariant and PathAI have exhibited remarkable accuracy in histological image analysis, surpassing or matching the performance of experienced pathologists in certain contexts (18, 19). However, these models are primarily trained on digital slide data, whereas LLMs such as ChatGPT-4o mini rely solely on textual input-output relationships. While ChatGPT lacks the capability to analyze microscopic images directly, its ability to synthesize information and provide differential diagnoses from textual data presents a unique opportunity for integration into pathology workflows.

Looking ahead, AI is expected to expand its role in pathology by enhancing real-time intraoperative consultations, automated grading of tumors, and even predicting therapeutic responses. However, for AI models like ChatGPT to reach their full potential in pathology, hybrid models that combine image analysis with natural language processing (NLP) will be necessary (20).

Our study compared the diagnostic accuracy of ChatGPT-4o mini with that of 15 experienced pathologists. The correct response rate demonstrated by ChatGPT-4o mini was 41.7%, which was significantly lower than the same rate of pathologists (78.06%). This performance gap is consistent with the results of previous studies that have evaluated AI models trained on non-image datasets, where the lack of image-based contextual understanding led to inferior diagnostic accuracy (21).

The error profile analysis revealed that low-impact diagnostic errors were observed in 33.3% of ChatGPT-4o mini's responses, whereas pathologists made similar errors at a rate of 6.9%. Additionally, ChatGPT's FN and FP rates were both 8.3%, compared to 0.5% and 8.8% for pathologists. These findings align with the studies highlighting that AI models often excel in detecting common patterns but may struggle with atypical or rare cases, leading to higher rates of misclassification (22).

Real-world practice always involves clinical, radiological, and demographic context. Adding such data would likely improve accuracy for both AI and humans. Therefore, future studies should aim to include multimodal data combining histopathological images with clinical context to more accurately reflect real-world diagnostic environments and to better assess the full potential of AI in pathology.

Our findings on ChatGPT-4o mini's diagnostic performance are largely consistent with recent studies conducted in different areas of pathology. In our series, the model achieved an accuracy of 41.7%, with a sensitivity of 60.0% and a specificity of 77.8%, whereas pathologists reached an average accuracy of 78.0%. Similarly, in the evaluation of oral mucosal lesions, ChatGPT's accuracy was reported as 52.5% compared to over 84% for experts; in glioma histopathology, accuracy was 43% for ChatGPT and 89% for neuropathologists; and in cervical cytology, ChatGPT achieved around 50% while pathologists exceeded 85% (11-13). Taken together, these results show that ChatGPT demonstrates similar limitations across organ systems and specimen types, particularly struggling with the recognition of complex morphological patterns, while human experts consistently achieve much higher levels of accuracy. At the same time, ChatGPT's most immediate value may not lie in primary diagnosis but rather in supportive roles such as simplifying pathology reports, education, and reducing workload (23). Our study reinforces these trends, confirming that ChatGPT cannot yet function as a standalone diagnostic tool but may, in the future, contribute to pathology practice through hybrid approaches.

The integration of AI into pathology workflows raises critical ethical considerations. The principle of "primum non nocere" (first, do no harm) is paramount in medical practice. To align with this principle, both ChatGPT-4o mini and human pathologists were given the option to refrain from making a diagnosis rather than providing a potentially misleading result. This aspect is particularly important in medical AI applications, where incorrect classifications may have serious implications for patient management and prognosis.

Moreover, the potential for AI-induced bias, over-reliance on technology, and the risk of automation bias require careful consideration. Regulatory frameworks and ethical guidelines must be continually updated to ensure that AI systems are deployed in a manner that minimizes harm and maximizes patient benefit (24, 25).

Our findings underscore the need for ongoing refinement of AI models in pathology, particularly through the integration of hybrid systems that combine histopathological image analysis with NLP capabilities. Such approaches could lead to the development of intelligent diagnostic assistants that not only flag suspicious findings but also facilitate diagnostic consensus among pathologists and contribute to reducing workload in high-volume settings.

To enhance the clinical utility of ChatGPT-like models, future efforts should focus on incorporating image interpretation algorithms capable of analyzing complex tissue patterns and morphological features. Equally important is the continued training of these models on large, diverse, and pathology-specific datasets, which would enable better handling of diagnostically challenging or rare cases. Moreover, implementing AI successfully in clinical practice will require rigorous validation in real-world settings to ensure safety, reliability, and generalizability across different institutions and diagnostic environments.

By addressing these areas, future iterations of AI systems may evolve into robust and trustworthy tools that complement the expertise of human pathologists, supporting but not replacing their critical role in the diagnostic process.

Study Limitations

While our study contributes valuable insights into the comparative diagnostic performance of ChatGPT-4o mini and pathologists, several limitations must be acknowledged. First, the number of images was deliberately limited to 24 to ensure feasibility for 15 busy pathologists, while still representing a balanced spectrum of normal tissues, benign lesions, and malignancies. In addition, the clinical application of AI in medicine remains an advancing field. Our results should be interpreted as exploratory rather than definitive. This study should be viewed as providing preliminary insights into the potential role of AI. We recognize that a larger and more diverse dataset would increase generalizability and have highlighted this point more explicitly. Second, ChatGPT-4o mini is not designed as an image-analysis tool. Our rationale for using it nonetheless lies in its accessibility, widespread popularity, and the fact that clinicians already experiment with its image-upload functionality. In this sense, the study does not claim to evaluate a dedicated histopathology AI system but rather assesses how a general-purpose, widely used tool performs under diagnostic conditions. Third, although interobserver agreement among the 15 pathologists was assessed using Fleiss' kappa (κ=0.13), this low level of agreement may reflect differences in diagnostic thresholds, interpretive experience, and uncertainty in borderline cases. This variability may have been further amplified by the absence of clinical and radiological information and by the use of static microphotographs rather than whole-slide images, conditions that are known to increase subjectivity in histopathological interpretation. The absence of clinical information likely affected both human and AI performance, particularly in borderline entities where morphology alone is insufficient for confident classification. In daily practice, even experienced pathologists rely on clinical and radiological context to resolve such ambiguity. Therefore, the observed error patterns should not be interpreted as isolated failures of either the LLM or the human observers, but rather as a consequence of intentionally decontextualized image-based assessment. It is important to note that the observed variability does not necessarily undermine the overall high accuracy observed at the group level.

Another unique aspect of our study is that neither ChatGPT-4o mini nor the pathologists were provided with any clinical information. Only static microscopic images were evaluated. Using 24 static microscopic images allowed us to standardize image presentation and better evaluate the results. However, this is a serious limitation. In routine clinical practice, pathologists assess entire slides, evaluating different criteria across different magnifications. The use of static images may limit the interpretation of diagnostic cues. This stands in contrast to routine diagnostic workflows, where clinical history, radiologic findings, and demographic information play a crucial role in guiding interpretation. Previous research has demonstrated that access to relevant clinical data significantly enhances diagnostic accuracy among pathologists, and similar improvements have been observed in AI systems when clinical context is incorporated. Olawade et al. (26) emphasized that the integration of multimodal information, including clinical data, is critical to improving the accuracy and reliability of AI systems in healthcare delivery, warning that the absence of such context can limit their diagnostic utility. Similarly, Obuchowicz et al. (27), in their review of AI applications in medical imaging, highlighted that combining clinical, radiological, and histopathological data substantially increases diagnostic accuracy compared to image-only analysis.

CONCLUSION

In conclusion, while ChatGPT's diagnostic accuracy was inferior compared to that of the pathologist's, its ability to identify partially correct responses and error profiles suggests its potential as a diagnostic assistant. The absence of clinical information in this study likely influenced diagnostic accuracy, highlighting the importance of integrating clinical context in future AI-assisted diagnostics. Future AI models that integrate image analysis and NLP may further enhance diagnostic accuracy and improve pathology workflows. Ethical considerations, including the principle of "primum non nocere" (first, do no harm), must guide the deployment of AI models in clinical settings to minimize harm and ensure patient safety.

Ethics

Ethics Committee Approval: *This study did not involve identifiable patient data. All histopathological images were de-identified archival cases and were used solely for research and educational purposes. According to institutional and international ethical guidelines, a formal approval from an ethics committee was therefore not required.*

Informed Consent: *All participating pathologists took part voluntarily and provided informed consent to contribute their diagnostic assessments.*

Footnotes

Conflict of Interest: *Preliminary results of this study were presented orally at the 3rd National Medical Student Symposium with the main theme "Foundations of Modern Medicine" held between November 30-December 1, 2024. The abstract was published in the symposium proceedings, and the presentation was awarded first prize. The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: J.M., Concept: J.M., Design: A.M., Data Collection or Processing: A.M., J.M., Analysis and/or Interpretation: A.M., J.M., Literature Search: A.M., J.M., Writing: A.M., J.M.*

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CASE REPORT

SURGICAL MANAGEMENT OF FEMORAL ARTERY PSEUDOANEURYSM FOLLOWING CORONARY ANGIOGRAPHY IN A COMPLEX COMORBID ELDERLY PATIENT: A CASE REPORT

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ABSTRACT

Femoral artery pseudoaneurysm is a significant complication of endovascular procedures, particularly in elderly and comorbid patients. This report aims to present a case of iatrogenic femoral artery pseudoaneurysm following coronary angiography in an elderly patient and to emphasize the importance of early diagnosis and appropriate intervention to prevent complications. A 70-year-old female with multiple comorbidities presented with right inguinal swelling and pain four months after undergoing coronary angiography via the right femoral artery. Imaging revealed a 31×40 mm pseudoaneurysm connected to the femoral artery. Due to symptom progression, surgical exploration was performed, and a 2 mm arterial wall defect was repaired with primary suturing. The postoperative course was uneventful. This case report emphasizes that early recognition and timely surgical management of pseudoaneurysms may prevent unfavorable outcomes and lead to favorable recovery.

Keywords: Coronary angiography, femoral artery, pseudoaneurysm

INTRODUCTION

Iatrogenic femoral artery pseudoaneurysm is a well-described complication following percutaneous vascular interventions such as coronary angiography (1). The incidence of pseudoaneurysm formation has become an increasingly common complication due to the growing prevalence of endovascular interventions (1-3). Risk factors include advanced age, the use of anticoagulants, large-bore catheterization, underlying vascular fragility, female sex, obesity, and low puncture site (4). While small-sized pseudoaneurysms can often be managed conservatively, surgical intervention becomes inevitable in complex cases (5). Vascular complications that arise after interventional procedures can significantly affect both the course of treatment and the prognosis (3). This case report presents the clinical course, diagnostic evaluation, and therapeutic approach in a patient who developed a femoral artery pseudoaneurysm following coronary angiography. The report highlights the importance of early recognition and appropriate management strategies in minimizing morbidity and optimizing outcomes in patients undergoing endovascular procedures.

CASE REPORT

A 70-year-old female with a history of diabetes mellitus type 2, secondary hypertension, chronic heart failure, atrial fibrillation (AF), hypothyroidism, an unruptured abdominal aortic aneurysm, a prior ischemic cerebrovascular event, and mitral and aortic valvular disease presented to Trakya University Emergency Department on March 10, 2023, with diffuse extremity pain. Her past surgical history included implantable cardioverter-defibrillator ablation three months prior, total abdominal hysterectomy with bilateral salpingo-oophorectomy ten years prior, and left foot surgery secondary to trauma 40 years prior.

On admission, the patient was found to be in AF, and bilateral pulmonary crackles were noted. Following diuretic therapy, findings regressed. Cardioversion was attempted with a 15-joule

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synchronized electrical shock under anesthesia. Although sinus rhythm was briefly achieved, AF recurred within one minute. Intravenous amiodarone was initiated, but sinus rhythm was not restored. The patient was informed and scheduled for follow-up.

On April 27, 2023, coronary angiography was performed via the right femoral artery. Four months later, on August 25, the patient presented with swelling in the right inguinal region. Ultrasonography revealed a pseudoaneurysm measuring 31×40 mm with a 4×5 mm neck connecting to the femoral artery. The diagnosis was confirmed by duplex Doppler ultrasound, which showed the classic "to-and-fro" waveform (6).

On September 7, the patient returned with worsening pain and swelling. Physical examination revealed palpable distal pulses. The cardiovascular surgery consultation did not indicate the need for emergent intervention. At outpatient follow-up on September 18, a pulsatile 5 cm mass was noted in the right inguinal region. Doppler ultrasonography confirmed arterial flow, and a pseudoaneurysm was diagnosed. The patient was hospitalized for definitive treatment.

On October 2, surgical exploration was performed under local anesthesia. A 6 cm incision over the femoral region exposed a pseudoaneurysm sac with a 2 mm arterial wall defect and active bleeding from the anterior surface of the superficial femoral artery (Figure 1). The pseudoaneurysm sac was completely excised, and the arterial defect was primarily repaired using 2/0 Prolene sutures (Figure 2). Hemostasis was confirmed, and a Hemovac drain was placed. The wound was closed in layers with Dexon and Prolene sutures.

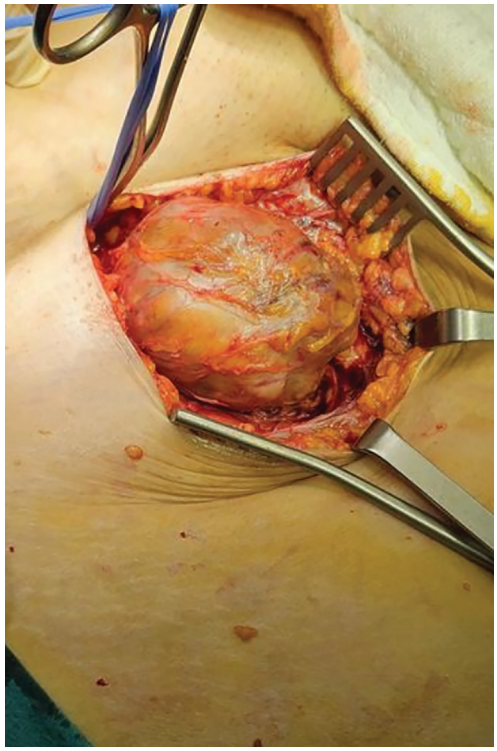

Figure 1: Intraoperative view showing the pseudoaneurysm sac.

As the patient had no recently implanted coronary stent, chronic warfarin therapy was discontinued upon admission, with a recorded international normalized ratio (INR) of 2.18, and daily INR monitoring was initiated. After the INR decreased to 1.75 on the fourth day of hospitalization, bridging anticoagulation with low-molecular-weight heparin (Clexane 0.6 mg, 2x1) was initiated. Surgery was performed once the INR reached a safe operative level of 1.2. The evening dose of low-molecular-weight heparin was withheld prior to surgery. Oral anticoagulation with warfarin (5 mg/day) was resumed on the first postoperative day. This therapy was continued in combination with Clexane (0.6 mg, 2x1) until discharge to maintain therapeutic INR levels, with daily INR monitoring. The patient was discharged with a therapeutic INR level above 2 following an uneventful postoperative course. Written informed consent was obtained from the patient to publish the case report.

DISCUSSION

Iatrogenic pseudoaneurysms represent significant vascular complications following percutaneous arterial interventions, most commonly associated with femoral artery catheterization (7). Unlike true aneurysms, pseudoaneurysms do not involve all three layers of the arterial wall (8). They have been reported in various vascular territories, including the femoral, popliteal, and brachial arteries, with the femoral artery - particularly distal to the bifurcation of the common femoral artery - being the most frequently affected site (8). The incidence ranges from 0.1% to 5.5%, but decreases significantly to approximately 0.02% when ultrasound guidance is employed during vascular access (8).

Several risk factors contribute to the development of pseudoaneurysms, including advanced age, female sex, use of anticoagulants, and the specific site of arterial access (8-10). Clinically, pseudoaneurysms often present with a pulsatile mass and localized symptoms such as ecchymosis and pain (4).

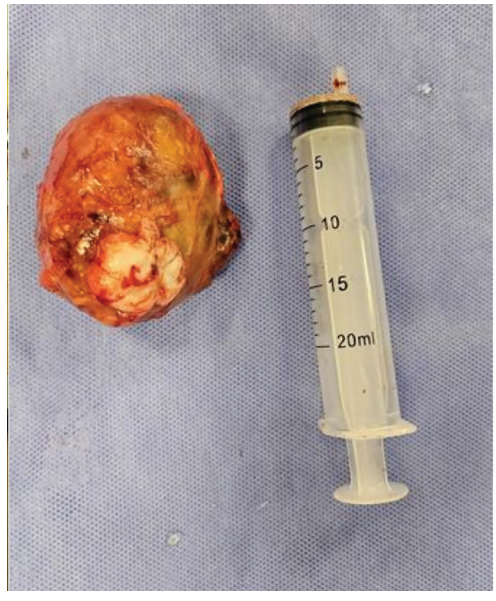

Figure 2: Excised pseudoaneurysm sac following surgical removal.

Diagnosis is primarily established using Doppler ultrasonography, which provides a detailed evaluation of pseudoaneurysm size and the presence of intraluminal thrombus (11).

Small pseudoaneurysms (<2 cm) often resolve spontaneously via thrombosis, whereas larger lesions typically require interventional treatment (8). In our clinical practice, open surgical repair is preferred for pseudoaneurysms with a neck diameter of ≥3 mm. This approach is particularly favored when the pseudoaneurysm sac remains active without evidence of intraluminal thrombosis and the risk of skin necrosis is present. A variety of therapeutic options are available. While surgical repair remains the gold standard in complex or refractory cases, minimally invasive approaches such as ultrasound-guided compression therapy and percutaneous thrombin injection have also proven to be effective (10). For instance, Samal et al. (10) reported four cases in which percutaneous thrombin injection was successfully performed under fluoroscopic guidance with temporary balloon occlusion, without any complications.

Previous reports of pseudoaneurysms in elderly and comorbid patients emphasize the critical importance of early diagnosis and a multidisciplinary management approach (12). Endovascular techniques are increasingly preferred due to their minimally invasive nature, and advanced methods such as ultrasonography-guided suture-mediated vascular closure devices and ultrasound-guided thrombin injection (UGTI) are considered highly effective treatments (13). In the case of pseudoaneurysms, treatment decisions should be individualized according to patient-specific risk factors, pseudoaneurysm characteristics, and available institutional resources. In this context, this case demonstrates that appropriate patient selection and timely intervention, especially in the face of acute threats such as impending skin necrosis or technical constraints, open surgical repair remains a safe and effective treatment option (12-14).

In the present case, the patient was on chronic anticoagulation therapy because of AF and had multiple comorbidities, including heart failure and a history of cerebrovascular events, contributing to a high overall bleeding risk. In anticoagulated patients, the likelihood of persistent flow through the pseudoaneurysm neck and incomplete thrombosis has been reported more frequently (15). Additionally, the pseudoaneurysm had a relatively wide neck (4×5 mm) and had progressively enlarged over serial examinations, both of which are known predictors of thrombin injection failure (15, 16). For these reasons, surgical repair was considered a safer and more definitive treatment option in this patient.

What distinguishes this case is the early recognition of the pseudoaneurysm in a patient with multiple complicating risk factors, including AF and ongoing anticoagulant therapy, which pose challenges to both diagnosis and management. The excision of the pseudoaneurysm sac under local anesthesia and primary repair of the artery demonstrates a personalized approach that balances patient safety with treatment efficacy.

The presence of anticoagulation is an important clinical factor that directly influences the choice of treatment for femoral artery pseudoaneurysms. Morphological characteristics of the pseudoaneurysm, such as neck width, size, and lobulation, are predictors of UGTI failure, with surgical repair being considered a more reliable option for wide-necked or symptomatic lesions (16). Although there are case series demonstrating successful UGTI even in patients receiving warfarin or direct oral anticoagulant therapy, ongoing anticoagulation requires a patient-specific risk-benefit assessment when deciding on management (14).

Studies have shown that pseudoaneurysms larger than 2 cm, those with a wide neck, those that rapidly expand, or those occurring in patients receiving therapeutic anticoagulation have lower success rates with ultrasound-guided compression or thrombin injection (15, 17). In such high-risk cases, surgical repair is considered a more definitive and reliable treatment option, which is consistent with the approach selected for our patient.

CONCLUSION

This case highlights the necessity of prompt diagnosis and the importance of individualized treatment planning to mitigate potentially life-threatening complications such as rupture or distal embolization. It emphasizes the essential role of interdisciplinary collaboration among cardiology, vascular surgery, and radiology teams in optimizing patient outcomes and the effectiveness of primary surgical repair in appropriately selected patients.

Ethics

Informed Consent: *Written informed consent was obtained from the patient for this study.*

Footnotes

Conflict of Interest: *The authors declare no conflict of interest.*

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CASE REPORT

PRIMARY SPLENIC DIFFUSE LARGE B-CELL LYMPHOMA WITH CD30 EXPRESSION: A RARE CASE REPORT

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ABSTRACT

Primary splenic diffuse large B-cell lymphoma represents a very uncommon manifestation within the spectrum of non-Hodgkin lymphomas, comprising approximately 1% of the total caseload. We report the case of an eighty-year-old male who presented with unintentional weight loss, fever, and night sweats. Laboratory studies revealed anemia, thrombocytopenia, and elevated inflammatory markers. Imaging demonstrated splenomegaly with a large hypodense lesion, while the mediastinal and hilar lymph nodes showed only mild uptake on positron emission tomography/computed tomography, which was interpreted as indicative of inflammation. Splenectomy revealed a necrotic mass measuring 13×12×10 cm that replaced most of the splenic parenchyma. Histology showed diffuse infiltration by large atypical lymphoid cells with immunoblastic morphology. Immunohistochemistry confirmed B-cell lineage (CD20, *PAX5*) with negativity for CD5, *BCL2*, CD10, and *c-MYC*. The Ki-67 index was markedly elevated (95%). Importantly, the tumor also exhibited aberrant CD30 expression, a finding reported in only a minority of cases of diffuse large B-cell lymphoma. While uncommon, CD30 positivity has been suggested in the literature to carry prognostic implications and may represent a biologically distinct subset. This case emphasizes the diagnostic and clinical significance of recognizing atypical immunophenotypic features in primary splenic diffuse large B-cell lymphoma.

Keywords: Diffuse large B-cell lymphoma, immunohistochemistry, non-Hodgkin lymphoma, splenic neoplasms

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) constitutes the most frequently diagnosed subtype among non-Hodgkin lymphomas (NHLs) (1). Splenic involvement is observed in approximately 20% of NHL cases; however, primary splenic DLBCL (PS-DLBCL) is extremely rare, accounting for approximately 1% of all lymphomas (2). Iannitto and Tripodo (3) proposed that splenic lymphomas may present with diverse clinical features and can be classified into three categories: asymptomatic patients with isolated splenomegaly, splenomegaly associated with alterations in peripheral blood counts, and splenomegaly accompanied by constitutional symptoms and abdominal discomfort. PS-DLBCL is challenging to diagnose due to its non-specific clinical presentation, and optimal management generally involves splenectomy followed by immunochemotherapy. DLBCL usually expresses pan-B-cell markers; occasionally, CD30, a marker classically associated with Hodgkin's lymphoma, may also be expressed in a subset of DLBCL cases (4). Herein, we report a rare case of PS-DLBCL with aberrant CD30 expression, highlighting its clinical, radiological, and immunohistochemical features.

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CASE REPORT

An eighty-year-old male patient was admitted to the internal medicine clinic with unintentional weight loss of 23 kg over the previous two months, accompanied by night sweats and fever. Laboratory evaluation revealed thrombocytopenia (platelets: $108\times10^3/mm^3$; reference range: $150\text{-}400\times10^3/mm^3$) and anemia (hemoglobin: 8.3 g/dL; reference range for male: 14-17,5 g/dL), while the white blood cell (WBC) count was within normal limits (WBCs: $7.81\times10^3/mm^3$; reference range: $4\text{-}10\times10^3/mm^3$). Inflammatory markers were elevated, including C-reactive protein (CRP) (CRP: 122 mg/L; reference range: 0-5 mg/L), along with increased urea levels (urea: 95 mg/dL; reference range: 20-55 mg/dL).

Abdominal ultrasonography revealed splenomegaly (157×87 mm) with a solid lesion measuring 128×85 mm. Computed tomography (CT) demonstrated a hypodense lesion of approximately 10 cm extending inferiorly from the lower pole of the spleen. Bilateral hilar and mediastinal lymph nodes, the largest measuring 2 cm, were within physiological limits, as confirmed by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/CT (PET/CT) The mild uptake observed in these nodes was interpreted primarily in favor of an inflammatory or granulomatous process (Figure 1A, 1B, 1C). In the hypodense mass extending approximately 10 cm inferiorly from the lower pole of the spleen, increased FDG uptake was observed, suggesting malignancy. Based on these findings, the splenic lesion was evaluated for malignancy, and splenectomy was performed.

On gross examination, the spleen measured 16×14×10 cm. On the cut surface, an irregularly bordered necrotic lesion measuring 13×12×10 cm was observed (Figures 2A, 2B). Microscopic examination revealed focal thickening of the splenic capsule. The splenic parenchyma was extensively infiltrated by atypical lymphoid cells with large nuclei, separated by fibrous septa containing broad areas of necrosis (Figure 3A). The infiltrating cells exhibited immunoblastic morphology, characterized by eosinophilic cytoplasm and atypical nuclei (Figure 3B). The surrounding parenchyma showed expansion of the red pulp and congestion.

Immunohistochemical analysis demonstrated that the atypical large cells expressed CD20 and *PAX5*, confirming a B-cell immunophenotype. CD5 negativity helped exclude mantle cell lymphoma and small lymphocytic lymphoma, while pancytokeratin negativity ruled out epithelial malignancies (Figure 4A). The diffuse growth pattern and the immunoprofile, particularly the absence of *BCL2* and CD10 expression, were not consistent with follicular lymphoma. Splenic marginal zone lymphoma (SMZL) was also considered in the differential diagnosis; however, the presence of large immunoblastic cells with a very high proliferative index (Ki-67: 95%), together with *BCL6*, MUM1, and *FOXP1* expression, was not consistent with SMZL, which typically demonstrates small to medium-sized marginal zone cells and an indolent immunophenotype. Aberrant CD30 expression was observed, whereas *c-MYC* expression was absent (Figure 4B). In the absence of peripheral or systemic lymph node involvement, the case was interpreted as primary splenic DLBCL, activated B-cell-like (ABC) type. An informed oral consent was obtained from the patient.

DISCUSSION

Primary splenic DLBCL is a distinctly uncommon clinicopathological entity, accounting for approximately 1% of all DLBCLs and less than 1% of NHLs (5). Although splenic involvement occurs in 20-40% of systemic lymphomas, true primary splenic disease is rare. Careful exclusion of systemic DLBCL and other entities, including T-cell/histiocyte-rich large B-cell lymphoma, SMZL, and peripheral T-cell lymphoma (PTCL), is therefore essential (4).

Typically, PS-DLBCL is diagnosed at a median age of sixty-four years (4). Our patient was eighty years old, representing the older end of the spectrum. Abdominal pain is the most frequently reported symptom (81%), followed by B symptoms (59%) (3, 4). Our patient presented with B symptoms, splenomegaly, anemia, and thrombocytopenia, broadening the clinical spectrum described in the literature. Furthermore, the hypodense splenic lesion detected on PET/CT correlated with underlying necrotic and fibrotic changes on pathological examination. According to the classification scheme of splenic lymphomas proposed by Iannitto and Tripodo (3), our patient can be categorized within the third group, characterized by splenomegaly associated with constitutional symptoms and abdominal discomfort.

Diffuse large B-cell lymphoma is characterized by large-cell morphology and a mature B-cell phenotype. It comprises two main subtypes: germinal center B-cell-like (GCB) and ABC. Although the 5th edition of the World Health Organization (WHO) Classification of Hematolymphoid Tumors states that the GCB/ABC classification has limited clinical impact, maintaining this distinction is recommended (6).

Histologically, PS-DLBCL is characterized by large atypical lymphoid cells with vesicular chromatin and prominent nucleoli (1). Immunohistochemical analysis typically demonstrates pan-B-cell markers such as CD20 and CD79a (7). In our case, the tumor cells expressed CD20 and *PAX5*, confirming B-cell lineage, and were negative for CD5, *BCL2*, and CD10, thereby excluding mantle cell lymphoma, small lymphocytic lymphoma, and follicular lymphoma. A more detailed evaluation of the differential diagnoses reveals that the most common clinical manifestations of mantle cell lymphoma are B symptoms or symptoms related to the involved lesion, although patients may also be asymptomatic at presentation. In addition, lymphocytosis may accompany the clinical findings. Mantle cell lymphoma typically demonstrates a CD5-positive B-cell phenotype characterized by expression of CD19, CD20, surface immunoglobulin M (IgM)/immunoglobulin D, and FMC-7, with light-chain restriction, reduced or absent CD23 expression, and strong cyclin D1 overexpression. In appropriate clinical settings, molecular workup may involve the determination of immunoglobulin heavy chain gene somatic

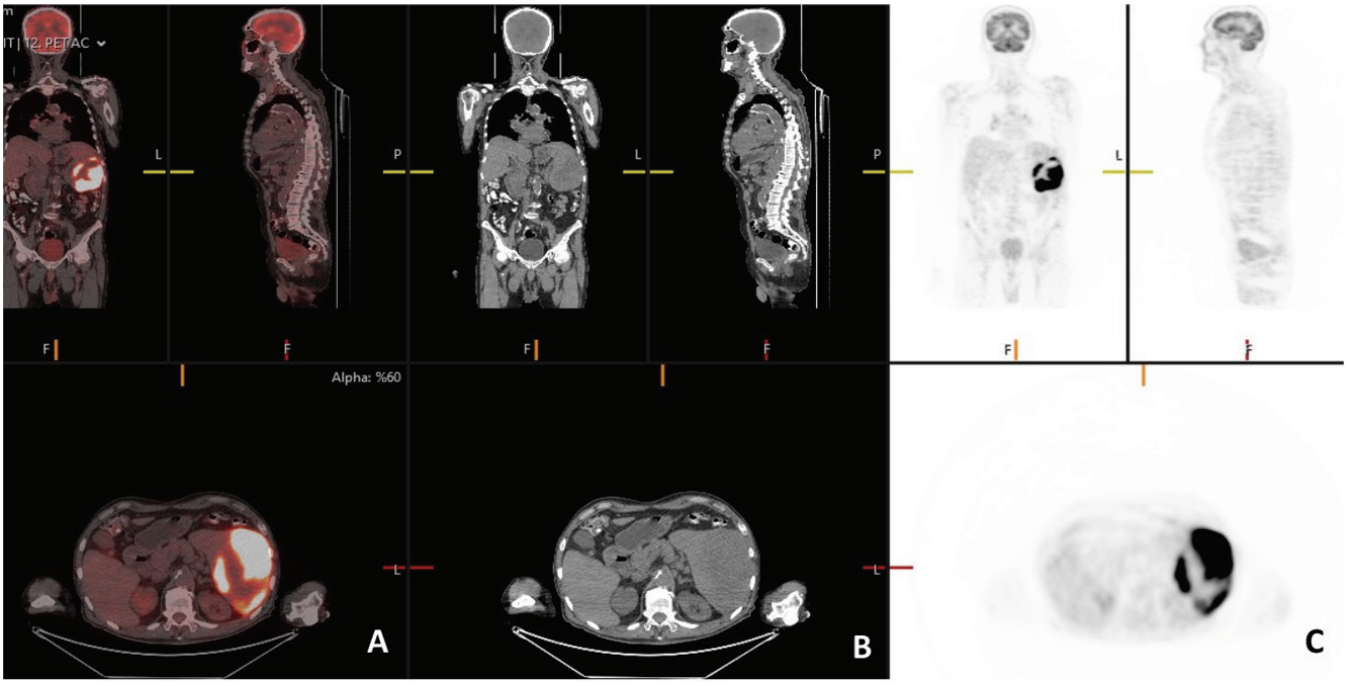

Figure 1: PET/CT (A), CT (B), and 18F-FDG PET/CT (C) scans show increased uptake localized to the enlarged spleen (SUV_{max} = 36.9), findings consistent with lymphoma.

PET/CT: Positron emission tomography/computed tomography, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, SUV_{max}: Maximum standardized uptake value

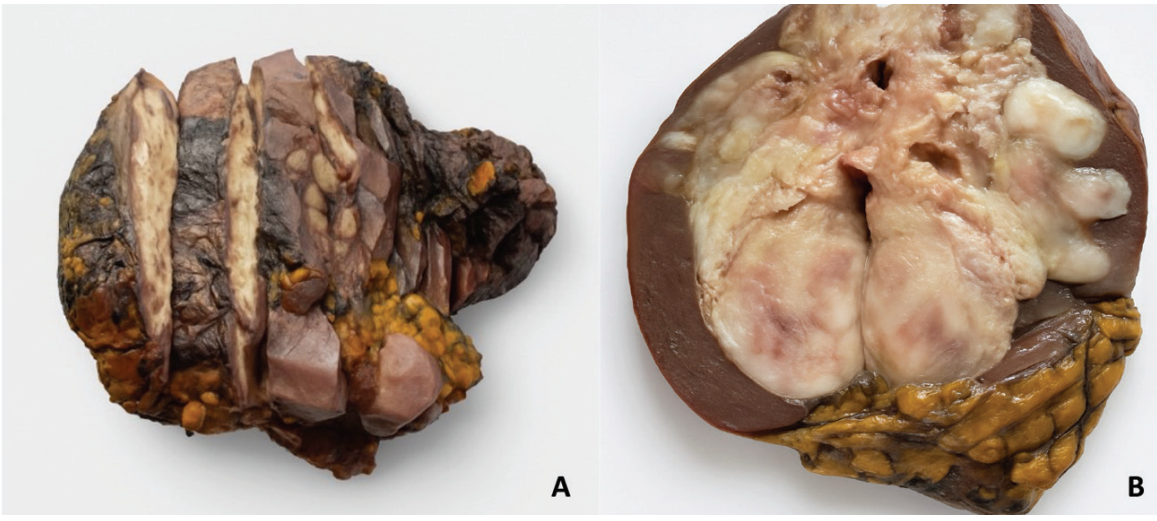

Figure 2: Gross appearance of the spleen. Increased weight and size with nodular areas on the outer surface of the capsule (A) and a solid mass with dirty-white nodular areas replacing the splenic parenchyma on the cut surface of the spleen (B) are shown.

mutation status and/or targeted next-generation sequencing for recurrent genomic alterations. Mutations involving *TP53*, *NOTCH1/2*, *SMARCA4*, *NSD2*, and *CCND1* have prognostic significance (8). Follicular lymphoma frequently presents with cervical or abdominal lymphadenopathy. While most patients are asymptomatic, symptomatic individuals may present with B symptoms and recurrent infections. Laboratory results are frequently unremarkable. Microscopic examination reveals incomplete or complete disruption of the lymph node architecture with multiple, comparably sized, nonpolarized neoplastic follicles and a thinned or missing mantle zone. Follicular lymphoma cells are positive for CD19, CD20, CD22, CD79, *PAX5*, and monotypic surface Ig (especially IgM). They also demonstrate germinal center markers such as CD10, *BCL6*, HGAL, *LMO2*, *STMN1*, GCET, and *MEF2B*. Commonly, cytogenetic analysis of follicular lymphoma cells identifies IGH-

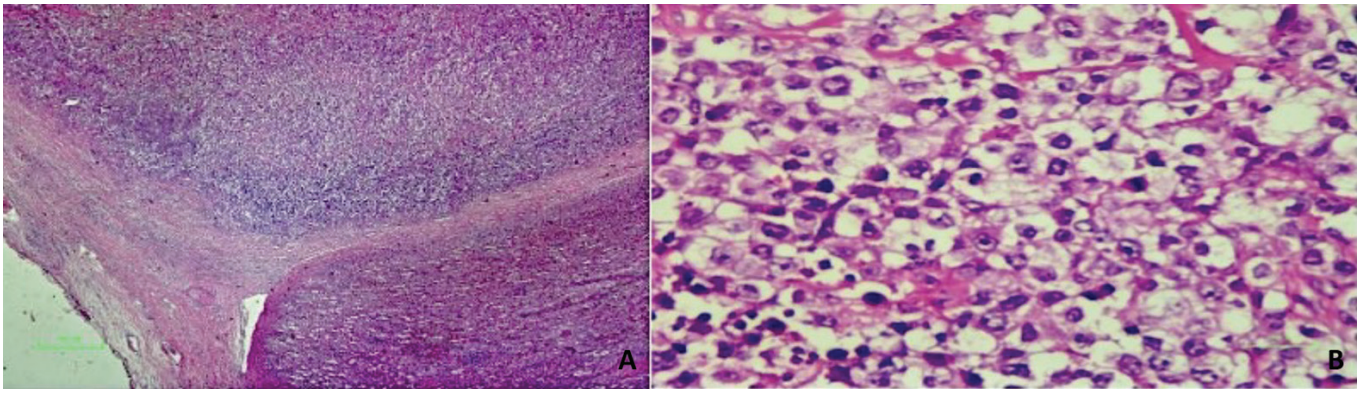

Figure 3: Microscopic examination. Low-power photomicrograph demonstrating nodular and diffuse infiltration of atypical lymphoid cells involving the splenic parenchyma and extending to the thickened capsule (H&E, ×40) (A). Microscopic view of diffuse large B-cell lymphoma demonstrating diffuse infiltration by large atypical lymphoid cells with immunoblastic morphology, vesicular chromatin, and prominent nucleoli (H&E, ×400) (B).

H&E: Hematoxylin and eosin

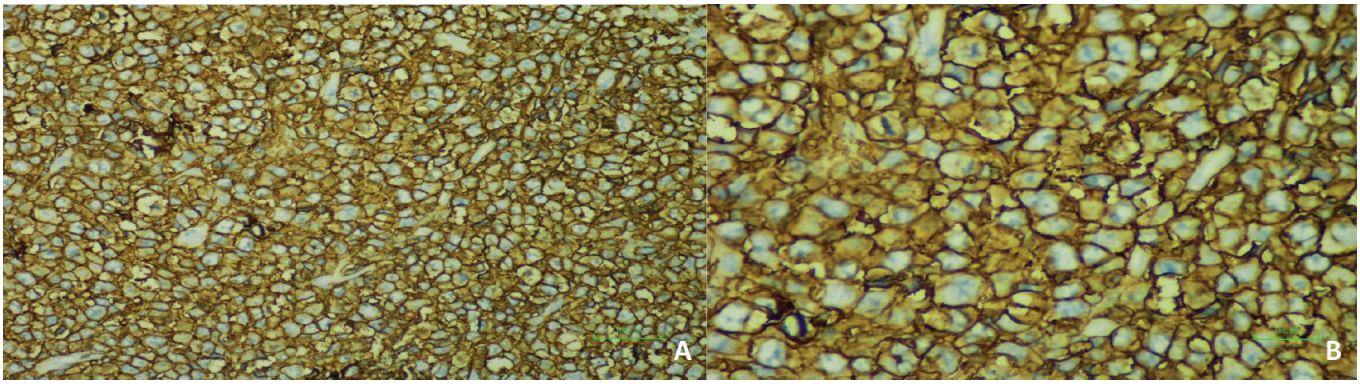

Figure 4: Immunohistochemical staining confirmed diffuse strong membranous CD20 expression in tumor cells (IHC, ×200) (A). Immunohistochemical staining confirmed strong membranous and cytoplasmic CD30 expression in tumor cells (IHC, ×400) (B).

IHC: Immunohistochemistry

BCL2 translocation, t(14;18) (q32;q21) (9). The clinical features of SMZL commonly include splenomegaly with bone marrow and peripheral blood involvement. Immunohistochemical examination demonstrates that SMZL cells express B-cell markers such as CD20 and *PAX5*, and are commonly positive for IgG and IgM and negative for germinal center markers. Genetic and molecular findings show that SMZL genetic abnormalities include alterations in apoptosis regulation, BCR and TNF signaling pathways, and nuclear factor kappa B (NF-κB) activation, involving genes such as *SYK*, *BTK*, *BIRC3*, *TRAF3*, *TRAF5*, *CD40*, and *LTB*. Differential diagnosis is guided by the examination of peripheral blood and bone marrow (10). In PTCL, patients present with constitutional symptoms. Microscopic examination reveals heterogeneous morphology and predominantly medium-sized or large cells with irregular nuclei and prominent nucleoli. Immunohistochemical analysis demonstrates that PTCL cells express pan-T-cell markers (CD3, CD2, CD5, CD7). Lack of *BCL2* expression, observed in 45-60% of cases, is considered a predictive marker of T-cell malignancies such as PTCL. Common genetic abnormalities include deletions of *CDKN2A* and *PTEN* (11).

In our case, aberrant expression of CD30 was observed, which is a feature reported in approximately 14% of DLBCL cases (12). While CD30 is classically associated with Hodgkin lymphoma and anaplastic large cell lymphoma (12, 13), its expression in DLBCL is less common and may have potential prognostic implications. In addition to its biological and prognostic implications, another important aspect of CD30 positivity is its role in the differential diagnosis between anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma and DLBCL. ALK-positive large B-cell lymphomas characteristically lack CD30 expression and are also frequently negative for CD20 (14).

Historically, splenectomy played a central role in both diagnosis and treatment of PS-DLBCL. With the introduction of rituximab, however, splenectomy is now primarily a diagnostic tool, while immunochemotherapy such as R-CHOP remains the standard of care (3, 15). Moreover, CD30 expression is not only relevant for differential diagnosis, but also for treatment plans. CD30 is a transmembrane glycoprotein exhibited by natural killer cells, dendritic cells, regulatory T-cells, and activated T-cells, and belongs to the tumor necrosis factor receptor superfamily (16). In light of its molecular structure, CD30 expression has shaped

new therapeutic strategies, such as the antibody-drug conjugate brentuximab vedotin (BV). In addition, studies have shown that CD30-positivity reflects important biological features, since high CD30 expression in tumor cells is associated with a characteristic immune landscape consisting of higher T-cell infiltration compared to CD30-low tumors. Additionally, within the tumor microenvironment, CD30 expression may influence the development of immunosuppressive or immunotolerant conditions (17). Based on these biological and pharmacological features, CD30-positive lymphomas have been associated with improved survival in some studies. Advances in CD30 targeted therapies consist of monoclonal antibody monotherapy, immunoconjugates (immunotoxins, radioimmunoconjugates, BV), bispecific antibodies, and CD30 chimeric antigen receptor T-cell therapy (18).

In our study, we used the Hans algorithm to classify the tumor as an ABC subtype, as it is the standard surrogate method recommended by the 5th edition of the WHO Classification of Hematolymphoid Tumors. To keep the diagnosis objective, we followed the common 30% cut-off for each marker. The subtyping was performed based on our immunohistochemistry results in a stepwise manner: first, the tumor cells were negative for CD10 (less than 30% expression), which ruled out the GCB subtype. Although *BCL6*-positivity was observed, the final classification was based on diffuse MUM-1 (*IRF4*) expression noted in the pathology report. Following the Hans decision tree, since the cells were CD10-negative and MUM-1-positive, the case was confirmed as a non-GCB/ABC phenotype (6). The ABC subtype is associated with a more adverse outcome following standard R-CHOP-based therapy compared with the GCB subtype, largely due to its constitutive activation of the NF-κB signaling pathway (17). Additionally, the presence of strong CD30 expression in the ABC background is a significant finding. It may define a unique biological group and, more importantly, it renders the tumor a potential target for antibody-drug conjugates like BV (19). By using the Hans criteria, we did not just label the subtype; we identified a phenotype that is crucial for deciding on modern treatments like polatuzumab vedotin (20).

CONCLUSION

Primary splenic DLBCL is an exceedingly rare entity, accounting for approximately 1% of all lymphomas and often posing diagnostic challenges. The present case highlights the diagnostic importance of thorough histopathological and immunophenotypic evaluation, particularly in an elderly patient with aberrant CD30 expression. It also contributes to the limited literature on this uncommon disease.

Ethics

Informed Consent: *An informed oral consent was obtained from the patient.*

Footnotes

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: M.A.M., D.T.T., Y.E.A., F.Ü., F.Ö.P., Concept: B.Ö., M.A.M., F.Ö.P., Design: B.Ö., M.A.M., Data Collection or Processing: D.T.T., F.Ü., F.Ö.P., Analysis or Interpretation: D.T.T., F.Ö.P., Literature Search: B.Ö., H.B.K., Writing: B.Ö., H.B.K., M.A.M., F.Ö.P.*

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